CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-429

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-429	Brand Name	Not provided
OCP Division (I, II, III, IV, V)	II	Generic Name	Cetirizine HCl
Medical Division	560	Drug Class	Antihistamine
OCP Reviewer	Yun Xu, Ph.D.	Indication(s)	Allergy, Hives Relief
OCP Team Leader (Acting)	Wei, Qiu, Ph.D.	Dosage Form	Capsule
		Dosing Regimen	Cetirizine 5 mg and 10 mg
Date of Submission	31 July. 08	Route of Administration	Oral
Estimated Due Date of OCP Review	March 15, 2009	Sponsor	Banner Pharmacaps Inc
PDUFA Due Date	June 1, 2009	Priority Classification	standard
Division Due Date	April 1, 2009		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments 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:				
Patients-				
single dose:				
multiple dose:				
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:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				

traditional design; single / multi dose:	x	2		Food effect was assessed via cross-study comparison.
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				**Biowaiver was requested for the 5 mg capsule. CMC team will review it.**
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2		

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	X	
Comments sent to firm ?		
QBR questions (key issues to be considered)	Is Cetirizine 10-mg capsule and Zyrtec 10-mg tablet bioequivalent at both fasted and fed conditions?	
Other comments or information not included above	Since the pivotal BE studies comparing the test formulation and list drug are critical, it is desirable to conduct DSI inspection on pivotal studies 20-219-SA and 20-220-SA. Study 20-219-SA: A single-dose, 2-period, 2-treatment, 2-way crossover pivotal bioequivalence study of Cetirizine 10-mg softgel under fasted conditions Study 20-220-SA: A single-dose, 2-period, 2-treatment, 2-way crossover pivotal bioequivalence study of Cetirizine 10-mg softgel under fed conditions **Clinical facilities:** [redacted] b(4) **Analytical sites:** [redacted] b(4)	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

Banner Pharmacaps Inc (BPI) submitted an NDA for Cetirizine HCl (Cetirizine 5 mg and 10 mg capsules), in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.54. The application relies on the safety and effectiveness of the reference listed drug (RLD), Zyrtec™ tablets, 5 mg and 10 mg. No efficacy/safety study has been conducted with Pharmacaps' cetirizine capsules.

Clinical pharmacology section contains the following studies:

Pivotal study:

1. Study 20-219-SA: A single dose, open-label, randomized, 2-period crossover study to compare bioequivalence between Cetirizine 10-mg capsule and Zyrtec 10-mg tablet at fasted condition in young healthy subjects. Study results (shown in the table below) prepared by BPI showed the 90% confidence interval for comparing the maximum exposure based on $\ln(C_{max})$,

and for total systemic exposure based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, is within the bioequivalence range of 80% and 125%. Therefore, the test formulation is bioequivalent to the RDL at fasted condition.

Table S3: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Cetirizine

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	347.7594	339.9893	102.29	95.81	109.20	0.9998	12.93
$\ln(AUC_{last})$	2631.9062	2585.3569	101.80	96.06	107.89	1.0000	11.47
$\ln(AUC_{inf})$	2681.7712	2635.7309	101.75	96.05	107.78	1.0000	11.38

[a] Geometric Mean for the Test Formulation (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio(%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

2. Study 20-220-SA: A single dose, open-label, randomized, 2-period crossover study to compare bioequivalence between Cetirizine 10-mg capsule and Zyrtec 10-mg tablet at fed condition in young healthy subjects. Study results (shown in the table below) prepared by BPI showed the 90% confidence interval for comparing the maximum exposure based on $\ln(C_{max})$, and for total systemic exposure based on $\ln(AUC_{last})$ and $\ln(AUC_{inf})$, is within the bioequivalence range of 80% and 125%. Therefore, the test formulation is bioequivalent to the RDL at fed condition.

Table S3: Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of Cetirizine

Dependent Variable	Geometric Mean[a]		Ratio (%)[b]	90% CI[c]		Power	ANOVA
	Test	Ref	(Test/Ref)	Lower	Upper		CV%
$\ln(C_{max})$	279.7276	276.0859	101.32	92.90	110.50	0.9934	17.64
$\ln(AUC_{last})$	2655.9442	2678.1237	99.17	96.28	102.15	1.0000	5.97
$\ln(AUC_{inf})$	2713.6279	2733.6557	99.27	96.37	102.25	1.0000	5.98

[a] Geometric Mean for the Test Formulation (Test) and Reference Product (Ref) based on Least Squares Mean of log-transformed parameter values
[b] Ratio (%) = Geometric Mean (Test)/Geometric Mean (Ref)
[c] 90% Confidence Interval

Additional study report:

1. Comparison Report 20-219-SA/20-220-SA: The PK parameters of Cetirizine 10-mg capsule obtained in study 20-219-SA and 20-220-SA were compared in parallel manner to assess the effect of food on the test formulation. Study results prepared by BPI showed food had a significant effect on the rate of absorption while C_{max} under fed condition is approximately 20% lower relatively to that under fast condition; but food did not have a significant effect on the extent of absorption while AUC_{last} and AUC_{inf} were similar between fed condition and fast condition.

Validation of the analytical method, individual raw data and pharmacokinetic results are included for study 20-219-SA and 20-220-SA.

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/s/

Yun Xu
9/19/2008 11:28:46 AM
BIOPHARMACEUTICS

Wei Qiu
9/25/2008 02:04:05 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY REVIEW

NDA:	22-429
Type:	505 b(2)
Generic Name:	Cetirizine Hydrochloride
Indication:	Temporarily relieves these symptoms due to hay fever or other respiratory allergies: runny nose, sneezing, itchy, watery eyes, itching of the nose or throat in adults and children 6 years and older.
Dosage Form:	Soft gel capsule
Strength:	5 mg, 10 mg
Route of Administration:	Oral
Dosing regimen:	Once daily
Applicant:	Banner Pharmacaps Inc.
OCP Division:	DCP2
Clinical Division:	Office of Nonprescription Products (ONP-560)
Submission Date:	July 31, 2008
Reviewer:	Yun Xu, M.D. Ph.D.
Team Leader:	Sally Choe, Ph. D.

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1 EXECUTIVE SUMMARY

1.1 Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology-2 (OCP / DCP-2) reviewed the Clinical Pharmacology information for NDA 22-429 submitted on July 31, 2008 and finds it acceptable.

1.2 Phase IV commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics findings

Cetirizine hydrochloride, the active component of Zyrtec®, is an orally active H_1-receptor antagonist. The sponsor submitted NDA 22-429 to seek approval for Cetirizine HCl Capsules, 10 mg & 5 mg, in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.54. This application relies on the Agency's finding of safety and effectiveness for the reference listed drug (RLD), Zyrtec HCl Tablets, 10 mg & 5 mg, the subject of NDA 19-835, held by Pfizer Labs/McNeil Consumer Healthcare.

There are no clinical safety and/or efficacy studies supporting this NDA. Two single oral dose bioequivalence (BE) studies (Study 20-219-SA and 20-220-SA) were conducted to compare the new formulation (test) and the marketed formulation (reference) of cetirizine hydrochloride at 10 mg in healthy subjects under both fasted (20-219-SA) and fed (20-220-SA) conditions. The sponsor requested a biowaiver for 5 mg strength and in support of this biowaiver request, an *in vitro* dissolution study was conducted to compare the dissolution of cetirizine hydrochloride 10 mg versus 5 mg soft gelatin capsules.

Division of Scientific Investigations (DSI) has conducted an audit on Study 20-219-SA and Study 20-220-SA. In the inspection memorandum dated March 11, 2009, it was stated that an aberrant internal standard response was identified in runs 6 and 7 in study 1001659 (20-219-SA). Consequently, accuracy of runs 6 and 7 in study 1001659 can not be assured and samples in runs 6 and 7 should have been re-assayed. As these samples have not been re-assayed, data generated in runs 6 and 7, which included data from subjects 217, 218, 219, 220, 221, 222, 223, and 224, should be excluded from the BE determination. The rest of the study data are deemed to be acceptable for review. Therefore, the data from runs 6 and 7 are excluded from the BE determination in this review.

The following tables list the results of BE studies between 10 mg Cetirizine HCl Capsule (test, lot no. P070119-B2) and 10 mg currently-marketed Zyrtec HCl Tablets (reference – lot no. 0070K07A) under fasted (Table 1) and fed (Table 2) conditions. Based on the results, the bioequivalence between the test formulation and the reference formulation has been demonstrated.

Table 1. Pharmacokinetic parameters and bioequivalence statistics of cetirizine following single oral dose administration of a 10 mg new capsule formulation (test) and currently-marketed 10 mg Zyrtec® tablet (reference) in healthy subjects under fasted condition.

PK parameters	Geometric Least Squares Mean		Test: Reference ratio	
	Test: 10 mg Capsule	Reference: 10 mg Zyrtec® tablet	Point estimate	90% Confidence Intervals
C_{max} (ng/mL)	347.73	329.83	1.05	96.28 – 115.48
$AUC_{0\text{-last}}$ (ng.hr/mL)	2607.71	2618.82	1.00	94.89 – 104.81
$AUC_{0\text{-inf}}$(ng.hr/mL)	2663.06	2672.64	1.00	94.97 – 104.84

Table 2. Pharmacokinetic parameters and bioequivalence statistics of cetirizine following single oral dose administration of a 10 mg new capsule formulation (test) and currently-marketed 10 mg Zyrtec® tablet (reference) in healthy subjects under fed condition

PK parameters	Geometric Least Squares Mean		Test: Reference ratio	
	Test: 10 mg Capsule	Reference: 10 mg Zyrtec® tablet	Point estimate	90% Confidence Intervals
C_{max} (ng/mL)	279.73	276.09	1.01	92.90 – 110.50
$AUC_{0\text{-last}}$ (ng.hr/mL)	2655.94	2678.12	0.99	96.28 – 102.15
$AUC_{0\text{-inf}}$(ng.hr/mL)	2713.63	2733.66	0.99	96.37 – 102.25

2 QUESTION BASED REVIEW

2.1 General Attributes/Background

2.1.1 Regulatory background or history

Cetirizine hydrochloride, the active component of Zyrtec®, is an orally active H_1-receptor antagonist. The sponsor submitted NDA 22-429 to seek approval for Cetirizine HCl Capsules, 10 mg & 5 mg, in accordance with Section 505(b)(2) of the Federal Food, Drug and Cosmetic Act and 21 CFR 314.54. This application relies on the Agency's finding of safety and effectiveness for the reference listed drug (RLD), Zyrtec HCl Tablets, 10 mg & 5 mg, the subject of NDA 19-835, held by Pfizer Labs/McNeil Consumer Healthcare. The proposed drug product, Cetirizine HCl Capsules, 10 mg & 5 mg, differs from the RLD in dosage form (capsule vs. tablet), and is otherwise similar with respect to route of administration, strength, and indications. The intended indication is to temporarily relieve these symptoms due to hay fever or other respiratory allergies:

runny nose, sneezing, itchy, watery eyes, itching of the nose or throat in adults and children ≥6 yrs of age.

2.2 General Clinical Pharmacology

2.2.1 Pharmacokinetics of Cetirizine Hydrochloride

According to the physician's insert of Zyrtec® tablet, the maximum plasma cetirizine concentration was reached at ~1 hour following oral administration of tablets. When healthy volunteers were administered multiple doses of cetirizine (10 mg tablets once daily for 10 days), a mean peak plasma concentration (C_{max}) of 311 ng/mL was observed. No accumulation was observed. Cetirizine pharmacokinetics is linear for oral doses ranging from 5 to 60 mg. The mean elimination half-life is 8.3 hours following oral administration of cetirizine in healthy subjects. Food had no effect on the extent of cetirizine exposure (AUC) but Tmax was delayed by 1.7 hours and C_{max} was decreased by 23% in the presence of food.

2.3 General Biopharmaceutics

2.2.2 Composition of the new capsule formulation

The proposed drug product is available as an [redacted], immediate-release, liquid filled soft gelatin, 10 mg & 5 mg capsule. Table 3 lists all the [redacted] active and inactive ingredients) of the drug product and their quantity in this new capsule formulation. b(4)

Table 3. The quantitative composition and function of each component in Cetirizine HCl 10 mg & 5 mg soft gelatin capsule

[redacted] Ingredient	Quality Standard	Function	Weight/Capsule	
			5 mg	10 mg
Cetirizine hydrochloride	EP	[redacted]	5.0 mg	10.0 mg
Polyethylene glycol, 400	NF			
Sodium Hydroxide	NF			
Purified Water	NF			
Total theoretical fill weight				
Total theoretical fill weight at the machine [redacted]				

b(4)

b(4)

2.2.3 Biowaiver for the 5 mg strength

In support of the biowaiver request for the 5 mg strength, an *in vitro* dissolution study was conducted to compare the dissolution of Cetirizine hydrochloride 10 mg versus 5 mg

soft gelatin capsules, and the dissolution profiles were comparable between the two strengths. Detailed review of the *in vitro* dissolution study and the biowaiver request can be found in the CMC review. With this biowaiver request, no *in vivo* bioequivalent study was conducted for the 5 mg dose

2.2.4 Bioequivalence between test and reference product

Two single-dose bioequivalence studies (Study 20-219-SA and 20-220-SA) were conducted to compare the new formulation (test) and the marketed formulation (reference) of cetirizine hydrochloride at 10 mg in healthy subjects under both fasted (20-219-SA) and fed study (20-220-SA) condition.

2.2.4.1 Study 20-219-SA: Fasted BE Study

Study 20-219-SA is a single-dose, open-label, randomized, 2-period crossover study comparing the rate of absorption and oral bioavailability of cetirizine hydrochloride 10 mg capsule (test) manufactured by the sponsor to an equivalent oral dose of the commercially available reference product, Zyrtec® HCl 10 mg tablet (reference) manufactured by Pfizer Inc., following an overnight fast of at least10 hours. Twenty-four (24) healthy subjects were enrolled. Dosing days were separated by a washout period of at least 7 days. During each study period, blood samples were obtained prior to and following each dosing at pre-dose (0) and at 025, 05, 0.75, 1, 1.5, 1.5, 2, 3, 4, 6, 10, l6, 24, 36, and 48 hours after dosing. A total of 32 blood samples were collected from each subject, 16 samples in each study period. Twenty-three (23) of the 24 subjects enrolled completed the study. Subjects 217, 218, 219, 220, 221, 222, 223, and 224 were excluded based on the DSI recommendation. Therefore, data from fifteen subjects were used in the BE analysis.

Plasma cetirizine concentration-time profiles following administration of the two treatments are shown in Figure 1.The mean PK parameters for the two formulations are summarized in Table 4. The statistical analyses of the plasma PK parameters of cetirizine are summarized in Table 5.

Figure 1: Mean plasma concentration-time profiles of cetirizine versus time by treatment (A: test 10 mg capsule formulation; B: reference Zyrtec® 10 mg tablet) in healthy subjects under fasted condition

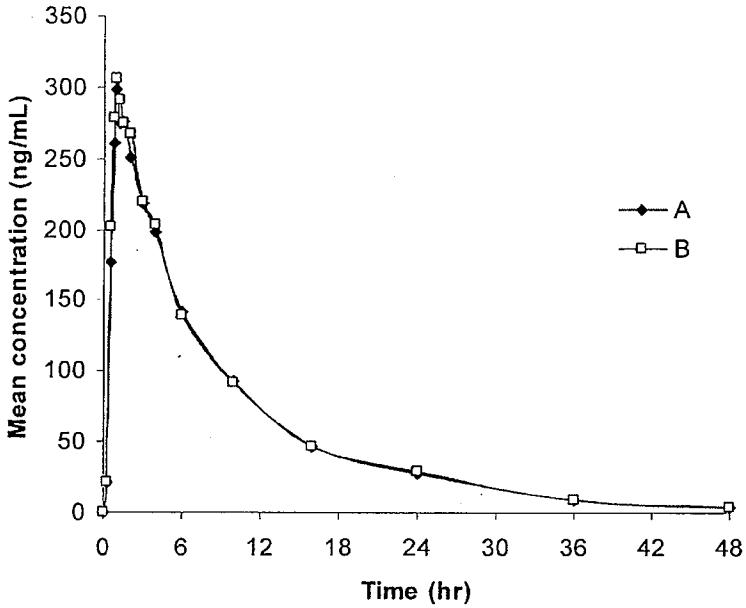

Table 4. Arithmetic mean plasma pharmacokinetic parameters of cetirizine following single oral dose administration of 10 mg capsule (test) and Zyrtec® 10 mg tablet(reference) in healthy subjects under fasted condition

Parameters	Test			Reference		
	N	Mean	SD	N	Mean	SD
Tmax (hr) *	15	1	(0,5,4)	15	1	(0.75,3)
Cmax (ng/mL)	15	356.86	84.69	15	341.16	96.72
AUClast (ng*hr/mL)	15	2678.11	606.71	15	2709.85	699.14
AUCinf (ng*hr/mL)	15	2734.31	615.64	15	2764.57	713.21
T1/2 (hr)	15	7.68	1.66	15	7.57	1.61

* Median and (Min. Max) was shown

Table 5. Statistical analysis of plasma pharmacokinetic parameters of cetirizine following single oral dose administration of 10 mg capsule (test) and Zyrtec® 10 mg tablet(reference) in healthy subjects under fasted condition

PK parameters	Geometric Least Squares Mean		Test: Reference ratio	
	Test: 10 mg Capsule	Reference: 10 mg Zyrtec® tablet	Point estimate	90% Confidence Intervals
C_{max} (ng/mL)	347.73	329.83	1.05	96.28 – 115.48
$AUC_{0\text{-last}}$ (ng.hr/mL)	2607.71	2618.82	1.00	94.89 – 104.81
$AUC_{0\text{-inf}}$ (ng.hr/mL)	2663.06	2672.64	1.00	94.97 – 104.84

The $AUC_{0\text{-inf}}$ and the $AUC_{0\text{-last}}$ were similar between the two formulations under fasted condition. The geometric means ratios were fully included within the 80-125% bioequivalence range. Similarly, 90% CI of the geometric mean ratio for C_{max} remained within the bioequivalence range of 80-125%.

Reviewer's Comments:

Subjects 217, 218, 219, 220, 221, 222, 223, and 224 were excluded based on the DSI recommendation. Data from fifteen subjects instead of 23 subjects that were evaluated in the study were used in the BE analysis under fasted condition. In a bioequivalence study, the range of the 90% confidence interval of the test to reference ratio will expand with decreased sample size. So it will be more difficult for the 90% confidence interval to remain within the bioequivalence range of 80-125% with smaller sample size. In this study, the 90% confidence intervals of the test to reference ratio for C_{max}, $AUC_{0\text{-last}}$, and $AUC_{0\text{-inf}}$ are within the range of 80-125% based on a reduced sample size of fifteen subjects. Therefore, it is concluded that the test formulation is bioequivalent to the reference formulation under fasted condition.

2.2.4.2 Study 20-220-SA: Fed BE Study

Study 20-220-SA is a single-dose, open-label, randomized, 2-period crossover study comparing the rate of absorption and oral bioavailability of cetirizine hydrochloride 10 mg capsule (test) manufactured by the sponsor to an equivalent oral dose of the commercially available reference product, Zyrtec® HCl 10 mg tablet (reference) manufactured by Pfizer Inc. under fed condition. Twenty-four (24) healthy subjects were enrolled. Dosing days were separated by a washout period of at least 7 days. Following an overnight fast of at least 10 hours, subjects consumed a standard high-calorie, high-fat breakfast meal that began 30 minutes prior to each dose. During each study period, blood

samples were obtained prior to and following each dosing at pre-dose (0) and at 025, 05, 0.75, 1, 1.5, 1.5, 2, 3, 4, 6, 10, l6, 24, 36, and 48 hours after dosing. A total of 32 blood samples were collected from each subject, 16 samples in each study period. All 24 subjects enrolled completed the study.

Plasma cetirizine concentration-time profiles following administration of the two treatments are shown in Figure 2. The mean PK parameters for the two formulations are summarized in Table 6. The statistical analyses of the plasma PK parameters of cetirizine are summarized in Table 7.

Figure 2: Mean plasma concentration-time profiles of cetirizine versus time by treatment (A: test 10 mg capsule; B: reference Zyrtec® 10 mg tablet) in healthy subjects under fed condition

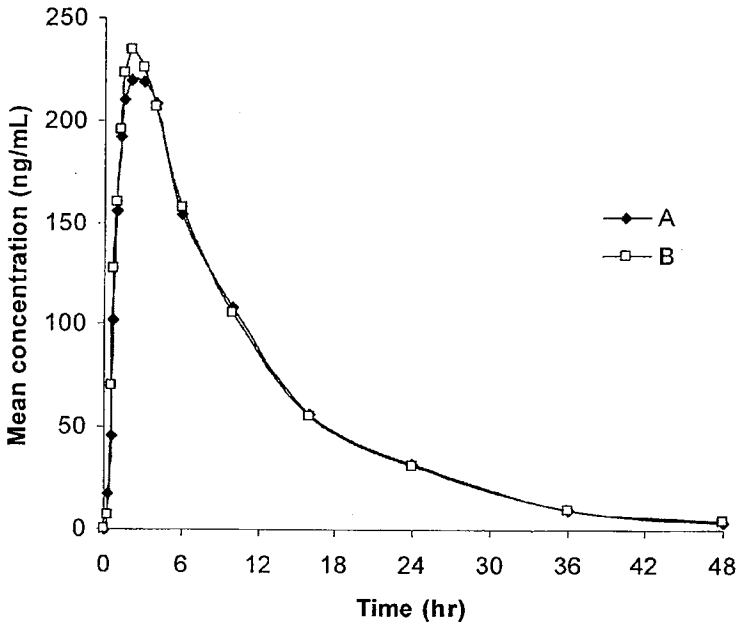

Table 6. Arithmetic mean plasma pharmacokinetic parameters of cetirizine following single oral dose administration of 10 mg capsule (test) and Zyrtec® 10 mg tablet (reference) in healthy subjects under fed condition

Parameters	Test			Reference		
	N	Mean	SD	N	Mean	SD
Tmax (hr) *	24	1.75	(0,5,6)	24	1.75	(0.75,4)
Cmax (ng/mL)	24	285.99	62.95	24	279.48	45.01
AUClast (ng*hr/mL)	24	2748.48	718.36	24	2768.24	730.23
AUCinf (ng*hr/mL)	24	2809.82	747.15	24	2828.83	764.63
T1/2 (hr)	24	7.53	1.45	24	7.43	1.61

* Median and (Min. Max) was shown

Table 7. Statistical analysis of plasma pharmacokinetic parameters of cetirizine following single oral dose administration of 10 mg capsule (test) and Zyrtec® 10 mg tablet(reference) in healthy subjects under fed condition

PK parameters	**Geometric Least Squares Mean**		**Test: Reference ratio**	
	Test: 10 mg Capsule	**Reference: 10 mg Zyrtec® tablet**	**Point estimate**	**90% Confidence Intervals**
C_{max} (ng/mL)	279.73	276.09	1.01	92.90 – 110.50
$AUC_{0\text{-last}}$ (ng.hr/mL)	2655.94	2678.12	0.99	96.28 – 102.15
$AUC_{0\text{-inf}}$ (ng.hr/mL)	2713.63	2733.66	0.99	96.37 – 102.25

The $AUC_{0\text{-inf}}$ and the $AUC_{0\text{-last}}$ were similar between the two formulations under fed condition. The geometric means ratios were fully included within the 80-125% bioequivalence range. Similarly, 90% CI of the geometric mean ratio for C_{max} remained within the bioequivalence range of 80-125%.

2.2.4.3 Comparison report for food effect on pharmacokinetics

The objective of this pharmacokinetic comparison was to assess the effect of a standard high calorie, high-fat breakfast meal on the rate and extent of absorption of the test formulation of cetirizine 10 mg soft gel capsule by the sponsor. Pharmacokinetic parameters of cetirizine obtained in two previous studies, Protocols 20- 219-SA (fasted condition) and 20-220-SA (fed condition), were compared in a parallel manner.

Plasma cetirizine concentration-time profiles following administration under fasted and fed conditions are shown in Figure 3. The mean PK parameters under fasted and fed condition are shown in Table 8. The statistical analyses of the plasma PK parameters of cetirizine under fasted and fed conditions are summarized in Table 8.

Figure 3. Mean cetirizine concentration- time profiles after administration of single oral dose 10 mg cetirizine soft gel capsule under fed conditions and fasted conditions

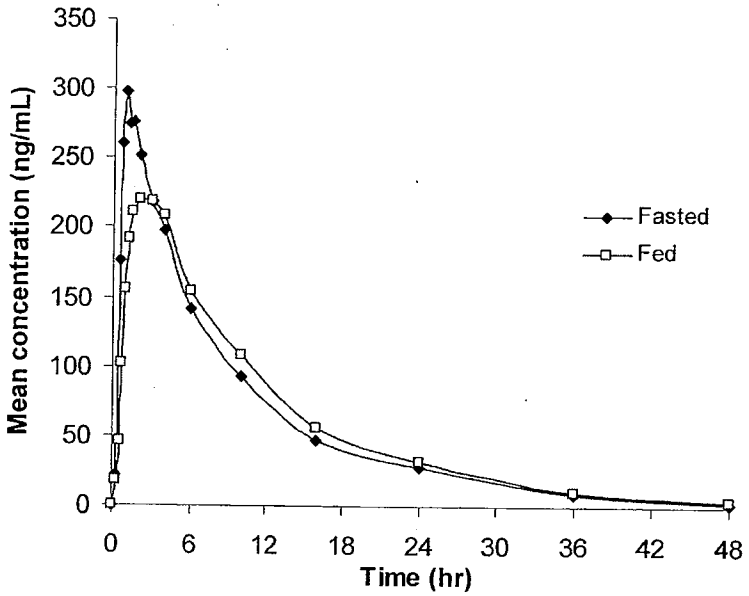

Table 8. Arithmetic mean plasma pharmacokinetic parameters of cetirizine following single oral dose administration of 10 mg cetirizine soft gel capsule under fed conditions and fasted condition

Parameters	Fasted			Fed		
	N	Mean	SD	N	Mean	SD
Tmax (hr) *	15	1	(0.5,4)	24	1.75	(0.5,6)
Cmax (ng/mL)	15	356.86	84.69	24	285.99	62.95
AUClast (ng*hr/mL)	15	2678.11	606.71	24	2748.48	718.36
AUCinf (ng*hr/mL)	15	2734.31	615.64	24	2809.82	747.15
T1/2 (hr)	15	7.68	1.66	24	7.53	1.45

* Median and (Min. Max) was shown

Based on the comparison, a high-fat meal has a significant effect on the rate of absorption of the test formulation of cetirizine (10 mg soft gel capsule); maximum cetirizine concentration under fed conditions is approximately 20% lower relative to the maximum cetirizine concentration under fasted conditions. However, a high-fat meal does not have a significant effect on the AUC from the test formulation; the oral bioavailability under fed conditions is comparable to the oral bioavailability under fasted conditions. This observation is consistent with the Zyrtec® tablet label.

Reviewer's Comments:

The sponsor used this comparison to demonstrate the food effect on the test formulation of cetirizine (10 mg soft gel capsule). Usually the Agency does not accept the cross-study comparison of food effect because of inter-study variability. Because the test formulation demonstrated bioequivalence to the reference formulation under both fasted and fed condition, the test formulation is expected to have similar food effect as that of reference formulation.

2.3.3 Did the sponsor use to-be-marketed formulation in the bioequivalence trial?

Yes. The formulation proposed for registration is the same as that used in the pivotal bioequivalence trial (study 20-219-SA and SA20-220-SA).

2.3 Analytical Section

2.3.1 Analytical assay performance

Cetirizine has been measured in plasma by using a validated method utilizing HPLC with MS/MS detection. The method was validated for a range of 2.00 to 500 ng/mL based on the analysis of 0.200 mL of plasma. Human plasma containing cetirizine, and the internal standards, cetirizine-D4, was extracted with an organic solvent (liquid-liquid extraction). Following centrifugation, the supernatant was transferred and dried. An aliquot of the extract was injected onto a SCIEX API 4000 LC-MS-MS equipped with a HPLC column. The peak area of the m/z 389 → 201 cetirizine product ion was measured against the peak area of the m/z 393 → 201 cetirizine-D4 internal standard product ion. Quantitation was performed using separate weighted linear least squares regression analyses generated from calibration standards prepared immediately prior to each run. The bioanalytical assay fulfilled the regulatory criterion [refer to the FDA guidance for industry "Bioanalytical Method Validation (Final-May 2001)] of not exceeding 15% (20% for the lowest QC samples) for precision and accuracy. Study samples were analyzed in runs containing calibrators and quality control samples, as recommended in the FDA guidance. Assay performance is summarized in Table 9.

According to the inspection memorandum by Division of Scientific Investigations (DSI), an aberrant internal standard response was identified in runs 6 and 7 in study 1001659 (20-219-SA). Consequently, accuracy of runs 6 and 7 in study 1001659 can not be assured and samples in runs 6 and 7 should have been re-assayed. As these samples have not been re-assayed, data generated in runs 6 and 7 (data for subjects 217, 218, 219, 220, 221, 222, 223, and 224) should be excluded from the BE determination. The rest of the study data can be acceptable for review. Therefore, the data from these subjects are excluded from the BE determination in this review.

Table 9. Bioanalytical Method Validation Summary for Cetirizine

Information Requested	Data
Bioanalytical Method Validation Report Location	Study 20-219-SA Pg 1206 of 1545 Study 20-220-SA Pg. 1274 of 1590 Module 5 section 5.3.1.2 (See Final Study Reports)
Analyte	Cetirizine
Internal Standard (IS)	Cetirizine-D4
Method Description	ATM-929; Liquid-liquid extraction; Sciex API 4000 LC-MS-MS
Limit of Quantitation	2.00, ng/mL
Average Recovery of Drug (%)	95.1
Average Recovery of IS (%)	94.9
Standard Curve Concentrations (ng/mL)	2.00, 4.00, 10.0, 25.0, 100, 250, 450, 500
QC Concentrations (ng/mL)	6.00, 100, 400
QC Intrarun Precision (% CV)	1.5 to 7.6
QC Intrarun Accuracy (% Bias)	-9.3 to -5.1
QC Inter-run Precision (% CV)	2.6 to 5.3
QC Inter-run Accuracy (% Bias)	-8.0 to -6.3
Bench-top Stability (hrs)	24 hours @ room temperature
Stock Stability (Reference Standard)	61 days @ 4 °C and 27 hours @ room temperature
Processed (Extract) Stability (hrs)	39 hours @ room temperature
Freeze-thaw Stability (cycles)	5 cycles
Long-term Storage Stability (days)	57 days @ -20 °C
Dilution Integrity	2500 ng/mL diluted 10-fold
Selectivity	No interfering peaks noted in blank plasma samples

3 LABELING RECOMMENDATIONS

From Clinical Pharmacology perspective, there are no changes to the submitted label.

4 APPENDIX

4.1 Proposed label by sponsor

7 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Yun Xu
3/30/2009 12:51:44 PM
BIOPHARMACEUTICS

Sally Choe
3/30/2009 02:37:40 PM
BIOPHARMACEUTICS

ONDQA (Biopharmaceutics) Review

NDA:	22429
Submission Date:	7/31/08
Product:	Cetirizine HCl Capsules (5mg, 10 mg)
Type of Submission:	Original NDA [505(b)(2)]
Sponsor:	Banner Pharmacaps Inc.
Reviewer:	Tapash K. Ghosh, Ph.D.

Background:

Background: Banner Pharmacaps Inc. (BPI) submitted a New Drug Application for Cetirizine HCl Capsules, 10 mg and 5 mg, in accordance with Section 505(b)(2) of the FD&C Act seeking approval for OTC marketing of the drug product. The application relies on the Agency's finding of safety and effectiveness for the RLD, Zyrtec® Tablets, 10 mg and 5 mg approved under NDA 19-835, held by Pfizer Labs/McNeil Consumer Healthcare.

BPI's proposed drug product (10 mg capsule) is bioequivalent to Zyrtec® (10 mg tablet), as demonstrated by the bioequivalence studies [20-219SA (Fasted BE study) and 20-220 (Fed BE study] performed by the contract research organizatior [redacted] No further clinical studies on the proposed drug product have been performed. b(4)

BPI requested a waiver for the proposed lower strength (5 mg capsules). According to BPI, this waiver request is based on comparative dissolution profile data (10 mg Capsules versus 5 mg Capsules) which were generated using the media, apparatus and testing methodology approved in the Zyrtec® NDA for quality control of the finished dosage form, as well as the compositional similarity between the 10 mg strength and the 5 mg strength. Of note, approved Zyrtec® dissolution methodology used water as the dissolution medium as opposed to BPI's proposed medium of pH 6.8 phosphate buffer.

Comments: The higher strength (10 mg) and lower strength (5 mg) capsules are proportionally similar. The dissolution profiles and the f2 values of these two strengths reveal similarity at pH 4.5 and 6.8. However, at pH 1.0, profiles differ at the 10 minute time point and the f2 value is lower than the acceptable value of 50. The profile comparison at pH 1.0 reveals that at 20 minute, the two profiles become similar again. As the sponsor's proposed dissolution specification is "Not less tha[redacted]t 30 minute at pH 6.8 buffer", and given that the higher strength (10 mg) capsule is bioequivalent with the 10 mg tablet (RLD), the difference in dissolution characteristic at the 10 minute time point at pH 1.0 only between 10 mg and 5 mg capsules should not have any impact on the bioavailability of the drug product. b(4)

Recommendation:

ONDQA has reviewed the biowaiver request for 5 mg Cetirizine HCl Capsules submitted in NDA 22249 on July 31, 2008. Provided the Office of Clinical Pharmacology review confirms that the proposed 10 mg capsules are bioequivalent with the Zyrtec® (10 mg tablet), ONDQA recommends granting biowaiver for the 5 mg strength based on comparative dissolution profiles, f2 values and other supporting documents submitted by the sponsor.

Tapash K. Ghosh, Ph. D.
Primary Reviewer

FT Initialed by Patrick Marroum, Ph. D. . _____

Review:

Formulation:

Ingredient	Amount (mg)/Capsule		Amount (%)/Capsule	
	10 mg	5 mg	10 mg	5 mg
Cetirizine HCl, EP	5	10		
Polyethylene glycol, 400 NF				
Sodium Hydroxide NF				
Purified Water NF				
Gelatin				
Glycerin				
Sorbitol Sorbitan				
Purified Water				
FD&C Yellow #6				
FD&C Red #40				
FD&C Blue #1				
[2]Total Dry Capsule Weight				

b(4)

b(4)

The following documents are provided and have been reviewed in connection with the biowaiver request for the 5 mg capsule strength:

Comparative Dissolution of Cetirizine Dihydrochloride Soft Gelatin Capsules versus Cetirizine Dihydrochloride Tablets (Zyrtec) (PD07-500):

This document describes the dissolution studies performed to compare the dissolution profiles of 10 mg cetirizine dihydrochloride soft gelatin capsules (Lot P0701 l9) manufactured at Banner Pharmacaps with 10 mg cetirizine dihydrochloride tablets (Lot 0070K07A) manufactured by Pfizer using the approved dissolution method for Zyrtec® (NDA 19-835) at pH 6.8 phosphate buffer medium using USP apparatus 2 (paddles) at 50 rpm at 37±0.5^{0}C. The results are as follows:

Dissolution Results (Percent Dissolved) - Banner Pharmacaps, Inc. Lot# P070119

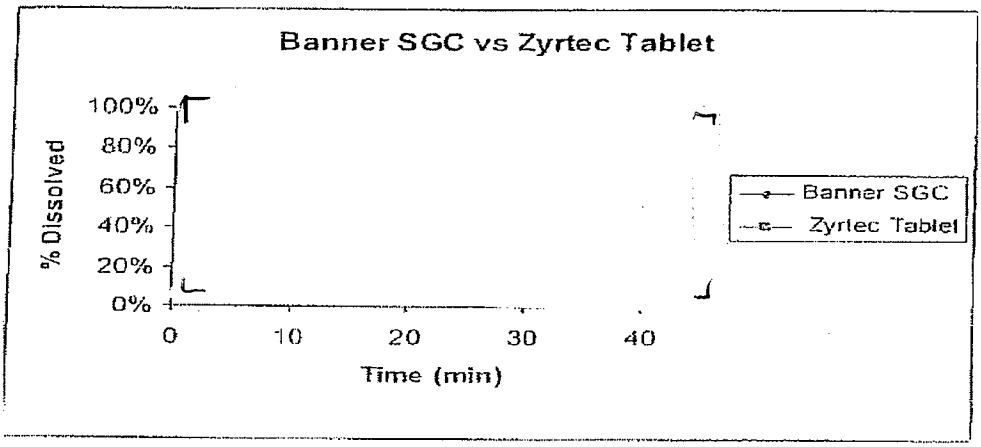
Time (min)	Capsule Number 1	2	3	4	5	6	7	8	9	10	11	12	Average (T)	Range	% RSD
10													22		37.5
20													95		2.1
30													98		1.3
45													99		1.7

b(4)

Dissolution Results (Percent Dissolved) - Pfizer Lot# 0070K07A

Time (min)	Tablet Number 1	2	3	4	5	6	7	8	9	10	11	12	Average (R)	Range	% RSD
10													89		8.4
20													93		6.4
30													95		5.3
45													96		4.6

b(4)



b(4)

Comments:

- *Please check the clinical pharmacology review for bioequivalency of 10 mg tablets and 10 mg capsules.*

Comparative Dissolution of Cetirizine Dihydrochloride 10 mg versus 5 mg Soft Gelatin Capsules at pH 6.8 (PD08-120):

This document describes the dissolution studies performed to compare the dissolution profiles of 10 mg cetirizine dihydrochloride soft gelatin capsules (Lot P0701 l9) with 5 mg (Lot P070605) capsules manufactured at Banner Pharmacaps at pH 6.8 phosphate buffer medium using USP apparatus 2 (paddles) at 50 rpm at 37±0.5^{0}C. The results are as follows:

Dissolution Results (Percent Dissolved) – 10 mg Lot# P070119

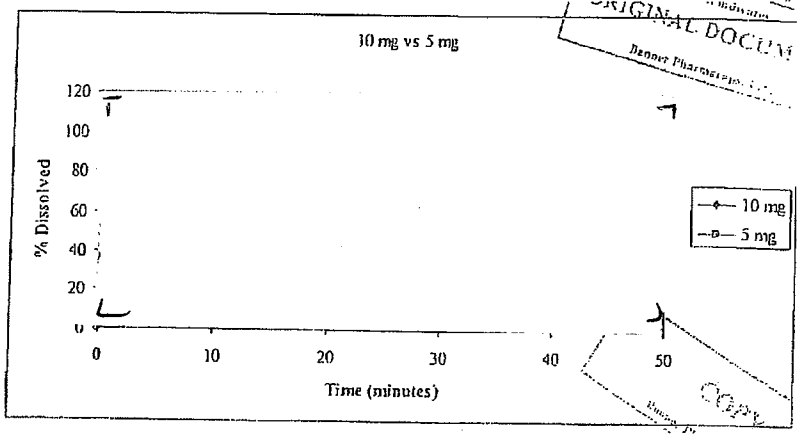
Time (min)	Capsule Number 1	2	3	4	5	6	7	8	9	10	11	12	Average (T)	Range	% RSD
10													22		37.5
20													95		2.1
30													98		1.3
45													99		1.7

b(4)

Dissolution Results (Percent Dissolved) – 5 mg Lot# P070605

Time (min)	Capsule Number 1	2	3	4	5	6	7	8	9	10	11	12	Average (R)	Range	% RSD
10													33		64.5
20													92		3.0
30													96		1.3
45													98		1.1

b(4)



b(4)

Comments:

The sponsor's f2 value is 61.2 showing similarity in dissolution profiles between the 10 mg and 5 mg strengths. The reviewer's calculated f2 is 58.5 excluding the 45 minute time point as the profile plateaued at 20 minute and therefore only one time point (30 minute) should be used in the f2 calculation.

Comparative Dissolution of Celirizine Dihydrochloride 10 mg versus 5 mg Soft Gelatin Capsules at pH 1 and 4.5 (PD08-477):

This document describes the dissolution studies performed to compare the dissolution profiles of 10 mg cetirizine dihydrochloride soft gelatin capsules (Lot P070119) with 5 mg (Lot P070605) capsules manufactured at Banner Pharmacaps at pH 1.0 and 4.5 phosphate buffer media using USP apparatus 2 (paddles) at 50 rpm at 37±0.5°C. The results are as follows:

pH 1

Dissolution Results (Percent Dissolved) – 10 mg Lot# P070119 pH 1

Time (min)	Capsule Number 1	2	3	4	5	6	7	8	9	10	11	12	Average (T)	Range	% RSD
10													56		52.6
20													96		2.3
30													96		2.0
45													97		1.9

b(4)

Dissolution Results (Percent Dissolved) – 5 mg Lot# P070605 pH 1

Time (min)	Capsule Number 1	2	3	4	5	6	7	8	9	10	11	12	Average (R)	Range	% RSD
10													86		13.3
20													95		1.5
30													96		1.1
45													96		1.3

b(4)

pH 4.5

Dissolution Results (Percent Dissolved) – 10 mg Lot# P070119 pH 4.5

Time (min)	Capsule Number 1	2	3	4	5	6	7	8	9	10	11	12	Average (T)	Range	% RSD
10													11		55.2
20													73		21.6
30													94		1.7
45													95		1.6

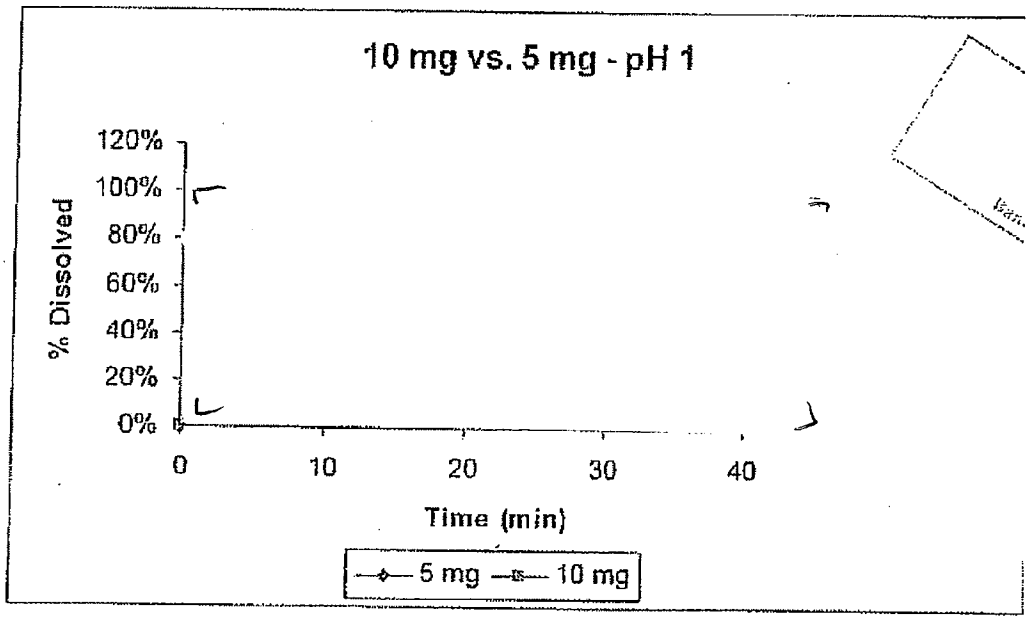
b(4)

Dissolution Results (Percent Dissolved) – 5 mg Lot# P070605 pH 4.5

Time (min)	Capsule Number 1	2	3	4	5	6	7	8	9	10	11	12	Average (R)	Range	% RSD
10													19		46.9
20													86		11.2
30													94		1.5
45													96		0.9

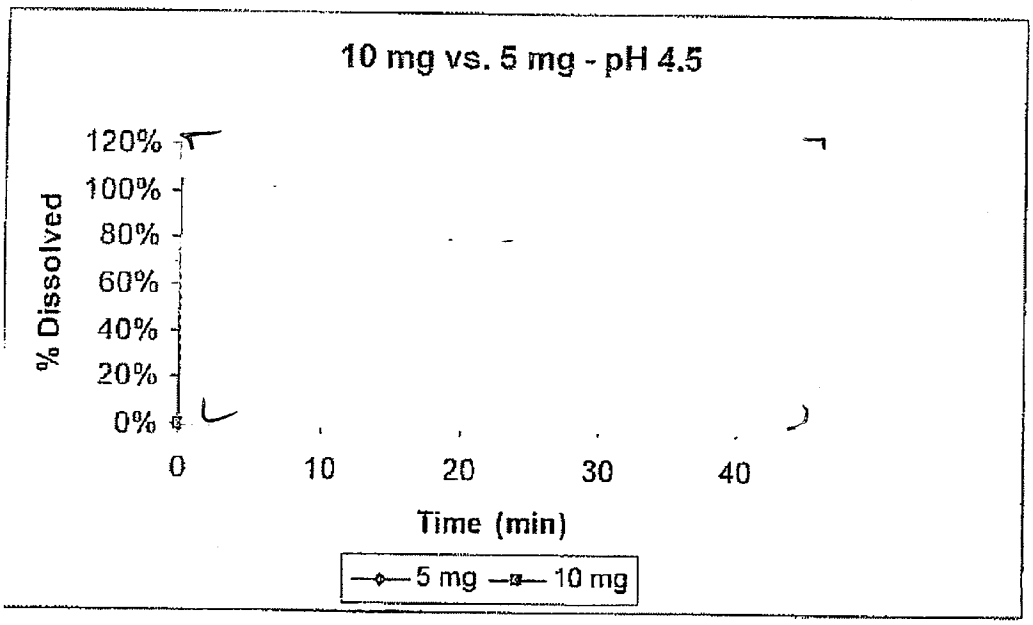
b(4)

pH 1



b(4)

pH 4.5



b(4)

f2 Values:

pH	1.0	4.5
Sponsor's f2	41.0	55.7
Reviewer's f2	38.0	55.7

Comments:

The sponsor's f2 value at pH 1.0 is 41.0 and is outside of the range identified as being similar. The reviewer's calculated f2 is 38.0 excluding the 45 minute time point as the profile plateaued at 20 minute and therefore only one time point (30 minute) should be used in f2 calculation. The reviewer agrees with the f2 values at pH 4.5

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/s/

Tapash Ghosh
1/22/2009 04:50:04 PM
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1/22/2009 04:51:21 PM
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