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APPLICATION NUMBER:

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA 22519 Addendum	April 21, 2011
Brand Name	Duexis
Generic Name	Ibuprofen /Famotidine
Reviewers	PeiFan Bai, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology and Inborn Errors Products
Sponsor	Horizon Therapeutics
Submission Type; Code	NDA 505 (b) (2), Original
Formulation; Strength(s)	Tablets; Ibuprofen 800 mg/famotidine 26.6 mg
Indication	For the treatment of the signs and symptoms of osteoarthritis, rheumatoid arthritis (b) (4) in patients at risk for developing NSAID-associated gastric ulcers
Dosing Regimen	One tablet, three times a day

This document is an addendum to the clinical pharmacology review of NDA 22519 which was filed in DARRTS on March 1, 2011. The sponsor conducted a single dose drug interaction study in 6 subjects using 800 mg ibuprofen and 40mg Pepcid and did not conduct the multiple-dose pharmacokinetic study to evaluate the pharmacokinetic parameters of both famotidine and ibuprofen components of Duexis. Since Duexis will be taken by the target population on a long-term basis, one key question from the safety point of view is whether famotidine exposure following multiple dose Duexis would be greater than that following a single dose Pepcid 40 mg, resulting in a greater degree of drug interaction with ibuprofen than what the sponsor has submitted. To address this concern, we have made an effort to estimate the multiple-dose AUC and Cmax values of famotidine following Duexis tid, compared with those following single Pepcid 40 mg, based on the data submitted in the NDA. Note that the target population is genetically heterogeneous, and that the drug interaction study only evaluates the systemic exposure of individual drug components delivered in a product.

Multiple dose AUC and Cmax of famotidine

The accumulation index (AI) of famotidine after multiple dosing is calculated using the equation of AI 1/(1-e $^{k\tau}$) where k is the elimination rate constant and τ dosing interval. The elimination constant calculated using k In2/t1/2 where t1/2 is 4.41 hr taken from

table 1 below is 0.157h-1. This elimination constant is used herein to calculate the steady state AUC and Cmax values of famotidine following multiple dose of oral Duexis tid. The accumulation index for Duexis famotidine component is 1.398.

The pharmacokinetic data of famotidine 26.6 mg in the presence of ibuprofen following oral administration of the HZT-501 (b) (4) (commercial formulation), adopted from section 2.2.2 in the clinical pharmacology NDA review, are listed below. This study results are used herein because the famotidine exposure was highest among all the studies submitted.

Table 1. Pharmacokinetic Parameters and Ratios of Computed Pharmacokinetic Parameters for Famotidine

	HZT-501 Fasted Mean (± SD)	HZT-501 Fed Mean (± SD)	Ratio B / A[1] (90% CI) %
n	27	27	
T_{max} (h)	2.02 ± 0.835	2.97 ± 1.07	--
C_{max} (ng/mL)	68.6 ± 29.3	58.1 ± 21.1	87.6 (77.9, 98.5)
$AUC_{0\text{-last}}$ (ng-h/mL)	429 ± 190	381 ± 122	92.4 (83.2, 102.6)
$AUC_{0\text{-inf}}$ (ng-h/mL)	439 ± 192	392 ± 121	92.8 (83.6, 103.0)
$t_{½}$ (h)	4.41 ± 1.22	4.23 ± 1.26	--

A single dose HZT 501 administered in fasted condition; B single dose HZT 501 administered within 30 minutes after commencement of consumption of a standardized high fat breakfast (fed condition).; AUC0 last means AUC0 24 hr.

The pharmacokinetic data of famotidine 40 mg from section 2.2.6 of clinical pharmacology review are listed below and the alone Cmax and AUC data are used.

Table 2. Pharmacokinetics Parameters (mean ± SD) for Ibuprofen (800 mg) and Famotidine (40 mg) When Administered Alone and In Combination (N 6)

Parameter	Ibuprofen		Famotidine	
	Alone	With Famotidine	Alone	With Ibuprofen
t_{max} (hr)	2.25 ± 1.89	1.58 ± 0.49	2.08 ± 1.02	1.75 ± 0.42
C_{max} (*)	51.9 ± 7.8	60.0 ± 10.9	136 ± 36.6	166 ± 41.0
AUC (**)	244 ± 63.5	242 ± 69.1	866 ± 234	1006 ± 215
$t_{1/2}$ (hr)	2.49 ± 0.54	2.33 ± 0.74	3.73 ± 0.35	3.92 ± 0.35

* ng/mL for famotidine; µg/mL for ibuprofen

** ng-h/mL for famotidine; µg-h/mL for ibuprofen

AUC (**)represents AUC0 infinity.

The estimated famotidine Cmax and AUC values following multiple dose Duexis tid are summarized below along with the actual Pepcid single dose data.

Table 3. Comparion of famotidine Cmax and AUC values following multiple dose Duexis tid and single dose Pepcid 40 mg

	Pepcid single dose (famotidine 40 mg)	Duexis tid Famotidine 26.6 mg
Cmax	136 ng/ml	95.92 ng/ml
AUC0-infinity	866 ng-h/ml	613.8 ng-h/ml

Summary: Our estimated steady state famotidine exposure (Cmax and AUC) following oral Duexis (26.6 mg famotidine plus 800 mg ibuprofen) is lower than that following single dose Pepcid, 40 mg.

Although the above comparison of famotidine exposure was based on data from different studies, there is supporting data from a head-to-head study in renal impairment patients which showed that famotidine exposure and t1/2 were comparable following single dose Duexis and Pepcid 26.6 mg suspension. These data implies that famotidine exposure following multiple dosing would be comparable between Duexis and Pepcid 26.6 mg.

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/s/

PEIFAN J BAI
04/22/2011

SUE CHIH H LEE
04/22/2011

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA: 22519	Submission Dates: March 30, 2010, September 7 & 21, 2010
Brand Name	Duexis
Generic Name	Ibuprofen /Famotidine
Reviewers	PeiFan Bai, Ph.D.
Team Leader	Sue-Chih Lee, Ph.D.
OCP Division	Division of Clinical Pharmacology 3
OND Division	Division of Gastroenterology Products
Sponsor	Horizon Therapeutics
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1 Executive Summary

1.1 Recommendation

The application is acceptable from the clinical pharmacology perspective provided that the sponsor adequately addresses the labeling comments and clarify how the drug was administered in relation to food intake in the Phase 3 trials.

The following should be communicated to the Medical Officer and sponsor: There is no information regarding how patients were instructed to take the proposed product during the Phase 3 trials. The sponsor should clarify for proper dosing instruction.

1.2 Phase IV Commitments

As a part of PREA requirement, the sponsor should conduct PK studies in pediatric population, 2-17 years of age if the application is approved.

1.3 Regulatory Background

This NDA a 505(b)(2) application, and the proposed product is a combination product. The reference products are Pepcid® for the famotidine component and Motrin® or Ibu® for the ibuprofen component. Ibu® was used after Motrin® was discontinued.

1.4 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The sponsor conducted all clinical pharmacology studies according to the agreement reached with the Agency, and the studies conducted are considered adequately designed.

Food effect: A high-fat meal reduced famotidine Cmax and AUC by approximately by 15% and 11%, respectively, and reduced ibuprofen AUC by approximately 14% but did not change Cmax, Food delayed famotidine Tmax and Ibuprofen Tmax by approximately 1 hr and 0.2 hr, respectively. The sponsor's proposed labeling statement of (b) (4) has been deleted by the review team because there is no information about how patients were instructed to take the proposed product during the clinical trials. So far, the Agency has not received clarification regarding this matter. Comments on drug administration with regard to food awaits sponsor's clarification.

Pharmacokinetic interaction: Co-administration of Pepcid and Motrin increased ibuprofen Cmax by 15.6% but did not change its AUC, and caused famotidine AUC and Cmax to increase 16% and 22%, respectively. Since both famotidine and ibuprofen components have been shown to be bioequivalent to their respective reference products, these slight pharmacokinetic interactions are for reference only and not relevant to dosing of the proposed product.

Bioequivalence comparison: For the approval of this NDA, the sponsor was required to demonstrate clinical efficacy of famotidine through phase 3 trials, so demonstration of famotidine bioequivalence between phase 3 and commercial formulations is sufficient. For the ibuprofen component, no clinical studies were conducted to demonstrate its clinical efficacy, so both its phase 3 and commercial formulations need to be bioequivalent to the reference product. For the ibuprofen component, each of the phase 3 and commercial formulations is orally bioequivalent to

the reference product, IBU®. For the famotidine component, phase 3 and commercial formulations is orally bioequivalent.

Renal impairment: An across-study comparison revealed that severe renal impairment did not change the pharmacokinetics of ibuprofen component but increased the Tmax, Cmax, AUC, and half life of famotidine by approximately 2 fold, 2 fold, 3.5 fold, and 2.5 fold, respectively. After referencing the approved labels of famotidine and ibuprofen, we recommend a statement of "Treatment with DUEXIS is not recommended in these patients with advanced renal disease." be added to the relevant sections in the proposed label.

DSI: Because clinical formulation and to-be-market formulation are different, the Clinical Pharmacology team requested a DSI regarding study HZ-CA-015, which was issued in August, 2010. The DSI review dated 22 February, 2011, was received through DARRTS on 25 February, 2011. There are no major issues raised by DSI reviewer that should preclude acceptance of study HA-CA-015 for review. Our review of study HZ-CA-015 still holds after re-analysis of bioequivalence comparison with subject 24 excluded per DSI reviewer's suggestion.

2 Question Based Review

2.1 General Attributes

2.1.1 What are the highlights of DUEXIS ® formulation?

DUEXIS is fixed-combination tablet of immediate-release ibuprofen and immediate-release famotidine. Each DUEXIS tablet contains ibuprofen, USP (800 mg) and famotidine, USP (26.6 mg).

2.1.2 What is the proposed indication?

DUEXIS, a combination of the NSAID ibuprofen and the histamine H2 -receptor antagonist famotidine, is indicated for the reduction of the risk of development of ibuprofen-associated, upper gastrointestinal ulcers in patients who require use of ibuprofen.

2.1.3 What are the proposed mechanisms of actions?

Ibuprofen possesses analgesic and antipyretic activities. Its mode of action, like that of other NSAIDs, is not completely understood, but may be related to prostaglandin synthetase inhibition. Famotidine is a competitive inhibitor of histamine H2-receptors. The primary clinically important pharmacologic activity of famotidine is inhibition of gastric acid secretion. Both the acid concentration and volume of gastric secretion are suppressed by famotidine, while changes in pepsin secretion are proportional to volume output.

2.1.4 What are the proposed dosage and route of administration?

One DUEXIS (ibuprofen 800 mg and famotidine 26.6 mg) tablet administered orally three times per day

2.1.5 What is the sponsor's dose selection rationale?

According to the sponsor, "By combining ibuprofen and famotidine into a single oral dosage formulation as HZT-501, co-administration of famotidine with ibuprofen reduces the incidence of ibuprofen-induced upper gastrointestinal ulceration while maintaining ibuprofen's analgesic and

anti-inflammatory efficacy." The approved doses of ibuprofen and famotidine are used for the development of a combination product.

2.1.6 What is the regulatory background?

This is a 505(b)(2) application.

Key Regulatory Milestones in the HZT-501 Development Program

Milestone	Date	Description/Outcome
Pre-IND meeting	June 13, 2005	Input on clinical and nonclinical issues was integrated into development plan.
US IND submission	Jan. 24, 2006	A Phase 1 study (Study HZ-CA-001) was initiated March 16, 2006.
EOP2 meeting	May 18, 2006 (minutes dated June 5, 2006)	Input on clinical, regulatory, and nonclinical issues was integrated into development plan.
SPA submitted for Studies HZ-CA-301 and HZ-CA-303	July 7, 2006 (SN 0004 & 0005)	Two pivotal Phase 3 studies were drafted to include the Agency's recommendations from the EOP2 meeting on May 18, 2006, and the protocols and SAPs were submitted for SPA.
SPA agreement	December, 19, 2006	The Agency responded on December 19, 2006 with written agreement to the SPAs.
EOP2 meeting	March 18, 2008 (minutes dated April 3, 2008)	Input on clinical pharmacology and CMC issues was integrated into development plan.

The Agency agreed at the EOP2 meeting on March 18, 2008 (meeting minutes dated April 3, 2008) that other ibuprofen products could be used as the reference listed drug (RLD) since the RLD Motrin had been discontinued.

According to the agreement at the March 18, 2008 EOP2 meeting (meeting minutes dated April 3, 2008), both the clinical and to-be-marketed formulations should be bioequivalent to the reference product with respect to the ibuprofen component. Since the Phase 3 combination tablet and commercial (b) (4) formulations of HZT-501 were bioequivalent with respect to famotidine, and both the Phase 3 combination tablet and the (b) (4) formulations of HZT-501 were bioequivalent to the reference product with respect to the ibuprofen component, Horizon did not conduct any additional relative bioavailability studies.

Because clinical formulation and to-be-market formulation are different, the Clinical Pharmacology team requested a DSI regarding study HZ-CA-015, which was issued in August, 2010. The DSI review dated 22 February, 2011, was received through DARRTS on 25 February, 2011. There are no major issues raised by DSI reviewer that should preclude acceptance of HA-CA-015 for review. Our review of study HZ-CA-015 still holds after re-analysis of bioequivalence comparison with subject 24 excluded per DSI reviewer's suggestion.

2.2 General Clinical Pharmacology

2.2.1 What are the design features of clinical pharmacology and clinical studies used to support the dosing and efficacy claim?

The designs of key individual studies conducted for this NDA are summarized below.

A. Food effect
A randomized, open-label, two-period, crossover study was conducted using the commercial formulation. A washout period of 14 days is adequate.

- Treatment Sequence 1: Period 1: fasted; Period 2: fed.
- Treatment Sequence 2: Period 1: fed; Period 2: fasted.

The FDA high fat breakfast with 966.2 calories was served 30 minutes before dosing.

	Eggs	Bacon	Potatoes	Toast	Milk	Butter
Fat (g)	11	7.8	16	1.8	8	19.2
Protein (g)	13	4.8	2	4.1	8	0.1
Carbohydrates (g)	1	0	28	26	11	0
Fat (cal)	99	70.2	144	16.2	72	172.8
Protein (cal)	52	19.2	8	16.4	32	0.4
Carbohydrate (cal)	4	0	112	104	44	0

B. Bioequivalence between ibuprofen comparator and its reference product (IBU®)
A randomized, 2-period, crossover, open label study was conducted. This study was conducted because a comparator tablet HZT-405 (800 mg ibuprofen) was used in a randomized, double-blind, active controlled efficacy and safety study. Subjects fasted for at lease 10 hrs overnight before dosing and continued for 4 hrs post dose. The washout period was 7 days.

C. Bioequivalence with respect to the components of ibuprofen and famotidine each between pairs of commercial (HZT-501 (b) (4)) and phase 3 formulations as well as ibuprofen reference product (IBU®):
A single center, randomized, open-label, three-period, six-sequence crossover study was conducted. For drug administration in each treatment period, subjects fasted for at lease 10 hrs overnight before dosing and continued for 4 hrs post dose. The washout period was 14 days between period 1 and period 2, and was 7 days between period 2 and period 3 for all sequences, and these washout periods are considered appropriate.

D. Drug interaction between ibuprofen and famotidine
Six healthy male subjects (21-34 years of age) participated in this randomized, crossover, open-label study. Subjects fasted overnight prior to drug administration and remained fasted after the 4-hr post dose blood sample was collected. Constituted as directed, PEPCID for Oral Suspension contained 40 mg of famotidine per 5 mL (from PEPCID label).

- Sequence 1. *Period 1*: ibuprofen 800 mg (Motrin®), followed 24 hr later by famotidine 40 mg. *Period 2*: concurrent administration of ibuprofen 800 mg and famotidine 40 mg.
- Sequence 2. *Period 1*: concurrent administration of ibuprofen 800 mg and famotidine 40 mg. *Period 2*: ibuprofen 800 mg, followed 24 hr later by famotidine 40 mg.

The washout period of 24 hrs between famotidine and ibuprofen is adequate since ibuprofen and famotidine each has a half life of less than 4 hrs. The 1 week interval between periods 1 and 2 for either sequence is adequate as well.

E. Relative bioavailabilities of ibuprofen and famotidine in HZT-501 tablets compared to concurrent administration of Motrin and Pepcid in renal impairment population
The phase 3 formulation of HZT-501 tablets was studied in a randomized, two-period cross-over, open-label study. Five white subjects with renal impairment participated (3 with severe and 2 moderate renal impairment). Creatinine clearance was determined based on the Cockroft-Gault formula, with < 30 ml/min as severe renal impairment and between 45 ml/min and 30 ml/min as moderate impairment. Subjects took a single dose of the study medication after an overnight fast of >10hrs and continued fasting until the 4-hr post dose blood sample was taken. The washout period of 1 week long is appropriate.

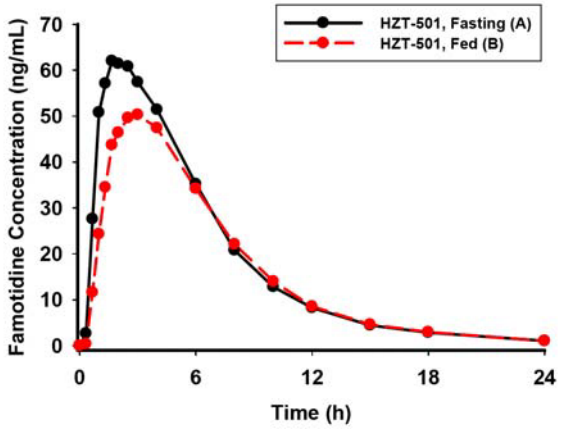
F. Phase 3 clinical trials. The sponsor submitted the results of two pivotal clinical trials, HZ-CA-301 and HZ-CA-303, to this NDA. Clinical site inspection identified site 389 of study 303 as problematic. Study 303 involves two sites, site 389 and site 363. The clinical review team has decided to disregard the data from site 389. The acceptance of site 363 data is pending awaiting the result of DSI. Regarding study 301, Dr. Wen Jen Chen's conclusion is that its statistic is not robust enough. Because of the major amendment issued in November, 2011 and many ongoing issues regarding the acceptance of partial data from study 303, we will defer the review conclusion of clinical studies to Dr. Ali Niak's final review. Dr. Niak is the medical officer of this NDA submission.

In summary, all clinical pharmacology studies were designed and studied properly.

2.2.2 Is there a food effect on the bioavailability of HZT-501?

With twenty eight (28) enrollments, 26 subjects completed the study (F: 13 & M: 13; mean age 33.7 years; mean BMI 24.5 kg/m^2).

Figure 1A Mean Plasma Concentrations of Famotidine versus Time



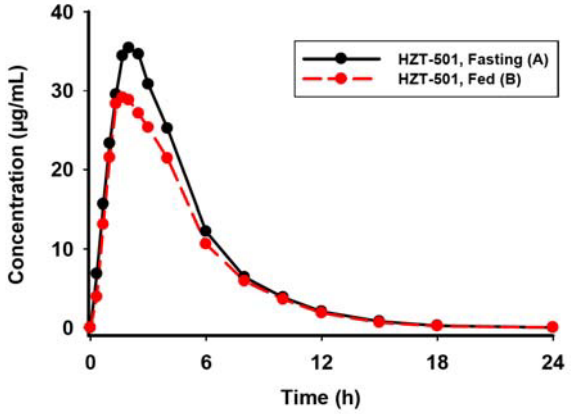
Pharmacokinetic Parameters and Ratios of Computed Pharmacokinetic Parameters for Famotidine

	HZT-501 Fasted Mean (± SD)	HZT-501 Fed Mean (± SD)	Ratio B / A[1] (90% CI) %
n	27	27	
T_{max} (h)	2.02 ± 0.835	2.97 ± 1.07	--
C_{max} (ng/mL)	68.6 ± 29.3	58.1 ± 21.1	87.6 (77.9, 98.5)
$AUC_{0\text{-last}}$ (ng-h/mL)	429 ± 190	381 ± 122	92.4 (83.2, 102.6)
$AUC_{0\text{-inf}}$ (ng-h/mL)	439 ± 192	392 ± 121	92.8 (83.6, 103.0)
$t_{½}$ (h)	4.41 ± 1.22	4.23 ± 1.26	--

A = single dose HZT-501 administered in fasted condition; B = single dose HZT-501 administered within 30 minutes after commencement of consumption of a standardized high-fat breakfast (fed condition).

A high-fat meal slightly delayed famotidine absorption and reduced its Cmax and AUC by approximately by 15% and 11%, respectively.

Figure 1B Mean Plasma Concentrations of Ibuprofen versus Time



Pharmacokinetic Parameters and Ratios of Computed Pharmacokinetic Parameters for Ibuprofen

	HZT-501 Fasted Mean (± SD)	HZT-501 Fed Mean (± SD)	Ratio B / A[1] (90% CI) %
n	27	27	
T_{max} (h)	2.05 ± 0.674	1.80 ± 0.924	--
C_{max} (µg/mL)	39.8 ± 6.48	38.5 ± 7.55	96.0 (89.0, 103.5)
$AUC_{0\text{-last}}$ (µg-h/mL)	182 ± 44.3	156 ± 40.2	85.4 (81.4, 89.7)
$AUC_{0\text{-inf}}$ (µg-h/mL)	184 ± 44.5	157 ± 40.3	85.4 (81.3, 89.6)
$t_{½}$ (h)	2.16 ± 0.449	2.00 ± 0.435	--

A = single dose HZT-501 administered in fasted condition; B = single dose HZT-501 administered within 30 minutes after commencement of consumption of a standardized high-fat breakfast (fed condition).

A high fat meal reduced ibuprofen AUC by approximately 14%, but the reduction did not cause the point estimate to fall out of the bioequivalence acceptance range of 80%-125%. In the approved label of Pepcid, it is stated that "Bioavailability may be slightly increased by food." Food reportedly did not significantly impact the bioavailability of either ibuprofen enantiomer (J Clin Pharmacol. 1992 Dec;32(12):1110-4.). Formulations could play a role in food effects.

In summary, a high fat meal did not cause famotidine AUC or ibuprofen AUC and Cmax to deviate from the bioequivalence acceptance range. Famotidine Cmax was out of the bioequivalence range. The sponsor's proposed statement of (b) (4) has been deleted by the review team since there is no clear instruction to the patients regarding Duexis administration during the clinical trials.

2.2.3 Is the comparator tablet HZT-405 (800 mg ibuprofen) bioequivalent to the reference product, IBU®?

Twenty two healthy subjects enrolled and completed the study (age: mean 26.8 ± 10.1 years; BMI : 24.3 ± 2.3 kg/m^2). Comparator ibuprofen tablets, instead of IBU (reference product), were used in the phase 3 clinical trials, HZ-CA-301 and HZ-CA-303 for the purpose of blinding. Therefore, establishment of bioequivalence between comparator ibuprofen tablets and IBU is needed. The pharmacokinetic results are summarized below.

Pharmacokinetics Parameters (mean ± SD) for Ibuprofen in Plasma Following Single Dose Oral Administration

Parameter	HZT-405	Commercially Available Ibuprofen 800 mg
t_{max} (hr)	1.71 ± 0.86	1.91 ± 0.57
C_{max} (µg/mL)	42.1 ± 7.0	39.2 ± 5.9
AUC (µg•hr/mL)	173 ± 41	168 ± 37
Half-life (hr)	2.20 ± 0.36	2.16 ± 0.43

90% Confidence Intervals for the Ratios of the Computed Pharmacokinetics Parameters for Ibuprofen in Plasma Following Single Dose Oral Administration

Parameter	Ratio[1]	Lower Limit	Upper Limit
C_{max} (µg/mL)	107.1	100.4	114.3
AUC (µg•hr/mL)	102.1	98.0	106.4

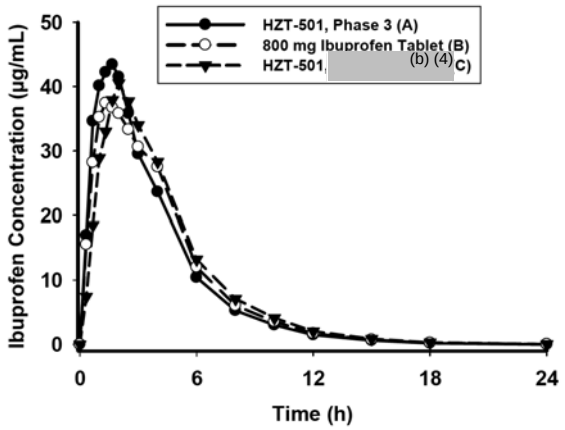
1 HZT-405 / ibuprofen 800 mg

The pharmacokinetic characteristics of ibuprofen were similar following a single dose of comparator product or IBU®. The 90% confidence intervals for Cmax and AUC fall within the bioequivalence acceptance range of 80%-125. It is concluded that the comparator tablet is bioequivalent to the reference product of ibuprofen.

2.2.4 Is ibuprofen bioequivalent across comparisons (phase 3 vs commercial, phase 3 vs IBU®, and commercial vs IBU®)?

Thirty-six (36) healthy subjects (48.5% male, 51.5% females) enrolled, and thirty three (33) subjects completed the study (Mean age: 29.6 years and mean BMI: 24.7 kg/m^2). Pharmacokinetic comparisons are summarized below.

Figure 2A Mean Plasma Concentrations of Ibuprofen versus Time



Pharmacokinetic Parameters and Ratios of Computed Pharmacokinetic Parameters for Ibuprofen in Plasma

	HZT-501 Phase 3 Formulation Mean (SD)	Ibuprofen 800 mg Mean (± SD)	HZT-501 (b) (4) Formulation Mean (± SD)	Ratio C / A[1] (90% CI) %	Ratio A / B[1] (90% CI) %	Ratio C / B[1] (90% CI) %
n	35	35	34			
T_{max} (h)	1.47 (± 0.705)	1.89 (± 1.05)	1.91 (± 0.616)	--	--	--
C_{max} (µg/mL)	55.0 (± 9.30)	49.6 (± 10.4)	44.9 (± 7.55)	81.5 (77.8, 85.3)	111.5 (106.5, 116.8)	90.9 (86.8, 95.2)
$AUC_{0\text{-last}}$ (µg-h/mL)	195 (± 37.9)	196 (± 38.9)	202 (± 39.5)	100.3 (97.2, 103.4)	99.7 (96.7, 102.8)	102.5 (99.4, 105.7)
$AUC_{0\text{-inf}}$ (µg-h/mL)	196 (± 38.0)	198 (± 38.7)	204 (± 39.6)	102.8 (99.7, 106.0)	99.7 (96.7, 102.8)	102.5 (99.4, 105.7)
$t_{½}$ (h)	2.21 (± 0.360)	2.16 (± 0.454)	2.23 (± 0.412)	--	--	--

A = single-dose HZT-501 Phase 3 formulation; C = single-dose HZT-501 (b) (4) formulation
B = ibuprofen (IBU®) 800 mg

The reviewer redid the bioequivalence analyses and confirmed the sponsor's results. When comparing the ibuprofen component of either Phase 3 or commercial formulation with ibuprofen (IBU®), the 90% confidence intervals for the point estimates (ratios) of Cmax and AUC0-last all fell within the bioequivalence acceptance range of 80%-125%. It is concluded that the ibuprofen component in phase 3 or commercial (b) (4) formulation is bioequivalent to ibuprofen (IBU®), the reference product. The commercial formulation had a lower ibuprofen Cmax compared to the phase 3 formulation or to ibuprofen (IBU®). With regard to ibuprofen component, the commercial formulation is bioequivalent to the reference product, but not to the phase 3 formulation. For the ibuprofen component, no clinical studies were conducted to

demonstrate its clinical efficacy of relieving pain, so both its phase 3 and commercial formulations need to be bioequivalent to the reference product for the approval of this NDA.

Bioequivalence comparison was reanalyzed by excluding subject 24 per DSI reviewer's comment (DSI report dated 22 February, 2011) and the results are summarized below.

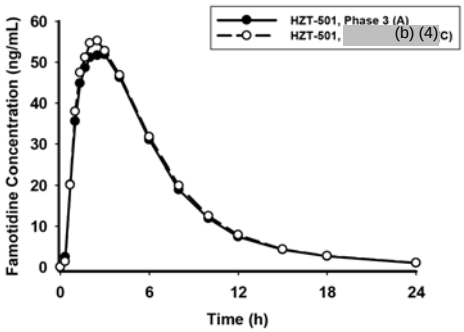
	Ratio C/A (90% CI)%	Ratio A/B (90% CI)%	Ratio C/B (90% CI)%
Cmax	81.08 (77.38-84.97)	111.28(106.21-116.59)	90.23 (86.11-94.54)
AUC last	103.34(100.25-106.53)	99.89 (96.9-102.96)	103.23 (100.14-106.41)

Reanalysis without subject 24's data did not change the bioequivalence outcome. Since the commercial formulation is bioequivalent to the reference product, the lack of bioequivalence between commercial and phase-3 formulation with respect to ibuprofen is not considered significant enough to jeopardize the approvability of this NDA.

2.2.5 Are commercial and phase 3 formulations bioequivalent with respect to famotidine?

Bioequivalence with respect to the famotidine component between phase 3 and commercial formulations was studied in the same study described in section 2.2.4, and the results are summarized below.

Figure 2B Mean Plasma Concentrations of Famotidine versus Time



Pharmacokinetic Parameters and Ratios of Computed Pharmacokinetic Parameters for Famotidine in Plasma

	HZT-501 Phase 3 Formulation Mean (± SD)	**HZT-501 (b) (4) Formulation Mean (± SD)**	**Ratio C / A[1] (90% CI) %**
n	35	34	
T_{max} (h)	2.21 (± 0.779)	1.99 (± 0.721)	--
C_{max} (ng/mL)	57.8 (± 18.1)	60.6 (± 22.5)	103.7 (95.8, 112.3)
$AUC_{0\text{-}last}$ (ng-h/mL)	374 (± 131)	387 (± 150)	103.6 (96.9, 110.9)
$AUC_{0\text{-}inf}$ (ng-h/ml)	385 (± 135)	397 (± 155)	103.3 (96.7, 110.4)
$t_{½}$ (h)	4.34 (± 1.11)	4.05 (± 0.958)	--

A = single-dose HZT-501 Phase 3 formulation; C = single-dose HZT-501 (b) (4) formulation

For the famotidine component, the sponsor demonstrated its clinical efficacy through a phase 3 trial, so demonstration of famotidine bioequivalence between phase 3 and commercial formulations is sufficient. The reviewer redid the bioequivalence analyses and confirmed the sponsor's results. The 90% confidence intervals for the point estimates (ratios) of Cmax and AUC0-last fell within the bioequivalence acceptance range of 80%-125%.

Bioequivalence comparison was reanalyzed by excluding subject 24 per DSI reviewer's comment (DSI report dated 22 February, 2011) and the results are summarized below.

Dependent	FormRef	Test	Ratio[%Ref]	CI_90_Lower	CI_90_Upper
Cmax	C	A	96.42	89.04	104.41
AUClast	C	A	96.51	90.21	103.26

Reanalysis without subject 24's data did not change the bioequivalence outcome.

It is concluded that the sponsor's phase 3 and commercial (b) (4) formulations are bioequivalent with respect to the famotidine component.

2.2.6 Is there drug interaction between famotidine and ibuprofen?

Six healthy male subjects (21-34 years of age) participated in this randomized, crossover, open-label study No body weight or BMI information was provided. Pharmacokinetic results are summarized below.

Pharmacokinetics Parameters (mean ± SD) for Ibuprofen and Famotidine When Administered Alone and In Combination (N 6)

Parameter	Ibuprofen		Famotidine	
	Alone	With Famotidine	Alone	With Ibuprofen
t_{max} (hr)	2.25 ± 1.89	1.58 ± 0.49	2.08 ± 1.02	1.75 ± 0.42
C_{max} (*)	51.9 ± 7.8	60.0 ± 10.9	136 ± 36.6	166 ± 41.0
AUC (**)	244 ± 63.5	242 ± 69.1	866 ± 234	1006 ± 215
$t_{1/2}$ (hr)	2.49 ± 0.54	2.33 ± 0.74	3.73 ± 0.35	3.92 ± 0.35

* ng/mL for famotidine; µg/mL for ibuprofen
** ng-h/mL for famotidine; µg-h/mL for ibuprofen

Compared to administration alone, co-administration slightly reduced the Tmax values of ibuprofen and famotidine, but increased the AUC and Cmax of famotidine by an average of 16% and 22%, respectively. Increases in famotidine AUC and Cmax are greater than the respective changes of ibuprofen. From the statistical point of view, the differences in both AUC and Cmax were not significant for either drug because of higher standard deviations. It is concluded that there is no significant pharmacokinetic interaction between ibuprofen and famotidine.

2.2.7 What are the respective relative bioavailabilities of ibuprofen and famotidine in HZT-501 versus concurrent administration of Motrin and Pepcid in renal impairment patients?

Five white subjects with renal impairment participated (mean age, 60.2 ± 11.1 years; mean BMI, 27.9 ± 3.4 kg/m2).

Creatinine Clearance, Renal Insufficiency Severity, and Diabetes Status of Enrolled Subjects

Subject ID	Creatinine Clearance (mL/min)	Renal Insufficiency Severity[1]	Diabetic?
01	20.41	Severe	Yes
02	26.32	Severe	No
03	34.78	Moderate	Yes
04	40.43	Moderate	Yes
05	29.43	Severe	No

1 Moderate = creatinine clearance 30-60 mL/min; severe = creatinine clearance < 30 mL/min. Creatinine clearance calculated by Cockroft-Gault formula.

Pharmacokinetics Parameters (mean ± SD) for Ibuprofen and Famotidine Following Oral Administration via HZT-501 and Following Concurrent Oral Administration of Equivalent Doses of Commercially Available Ibuprofen and Famotidine

Parameter	Ibuprofen		Famotidine	
	HZT-501[1]	Motrin[2]	HZT-501[1]	Pepcid[3]
t_{max} (hr)	2.10 ± 1.27	2.47 ± 3.11	5.30 ± 2.11	3.60 ± 1.52
C_{max}[4]	45.1 ± 24.9	48.1 ± 21.1	110 ± 44.9	101 ± 40.1
$t_{1/2}$ (hr)	2.47 ± 0.850	2.61 ± 0.975	11.4 ± 3.20	13.6 ± 6.28
AUC[5]	178 ± 98.2	198 ± 79.8	1674 ± 689	1790 ± 951

1 tablet containing ibuprofen 800 mg and famotidine 26.6 mg; 2 tablet containing ibuprofen 800 mg; 3 suspension containing famotidine 26.6 mg; 4 µg/mL for ibuprofen; ng/mL for famotidine; 5 µg*hr/mL for ibuprofen; ng*hr/mL for famotidine

In renal impairment patients, the proposed product had lower AUC and Cmax of ibuprofen compared to co-administration of Motrin and Pepcid (14% and 13% lower, respectively). Nevertheless, the Cmax and AUC of famotidine did not differ much between HZT-501 and Pepcid and Motrin; HZT-501 resulted in 8% lower and 6% higher, respectively, as compared to concurrent administration of reference products.

The 90% Confidence Intervals for the Ratios of the Computed Pharmacokinetics Parameters for Ibuprofen and Famotidine Following Oral Administration of HZT-501 and Following Concurrent Oral Administration of Equivalent Doses of Commercially Available Ibuprofen and Famotidine

Parameter	Ibuprofen			Famotidine		
	Ratio[1]	Lower Limit	Upper Limit	Ratio[2]	Lower Limit	Upper Limit
C_{max}[3]	86.9	60.0	125.8	115.8	83.1	161.4
AUC[4]	85.5	65.1	112.1	103.9	78.4	137.9

1 HZT-501 / ibuprofen 800 mg; 2 HZT-501 / famotidine 26.6 mg; 3 µg/mL for ibuprofen; ng/mL for famotidine; 4 µg*hr/mL for ibuprofen; ng*hr/mL for famotidine

Due to the small number of subjects, this study is not considered for bioequivalence comparison. Based on the bioequivalence results of another study using IBU® in healthy subjects, both commercial and phase 3 formulations are bioequivalent to the reference product.

Reviewer's comments:
Ibuprofen is eliminated following biotransformation to glucuronide conjugate metabolites that are excreted in urine, with little amount being eliminated unchanged (Clin Pharmacokinet. 1998 Feb;34(2):101-54. Clinical pharmacokinetics of ibuprofen:The first 30 years). Based on the pharmacokinetic characteristics of ibuprofen, little effect of renal impairment on ibuprofen is anticipated. According to the approved labeling of Motrin under NDA 017463, treatment with MOTRIN tablets is not recommended in these patients with advanced renal disease. Long-term use of NSAIDs can cause renal injury.

PEPCID is eliminated by renal (65-70%) and metabolic (30-35%) routes. Its renal clearance is 250-450 mL/min, indicating some tubular excretion (drug@FDA). According to the approved labeling of famotidine under NDA 19-527, for patients with creatinine clearance less than 10 mL/min, the elimination half-life of PEPCID may exceed 20 hours. It is recommended that in patients with moderate or severe renal insufficiency, the dose of PEPCID may be reduced to half the dose or the dosing interval may be prolonged to 36-48 hours.

Additional analyses were performed for either drug in patients with severe renal impairment and the results are shown below.
Mean (CV%) pharmacokinetic parameters of ibuprofen in severe renal impairment

	Tmax (h)	Cmax	AUClast	T1/2 (h)
HZT-501	1.72 (55%)	49.7 (66.8%)	201 (62%)	2.86 (22.8%)
RLDs concurrent	0.89 (21.6%)	56.3 (44.6%)	213 (43.8%)	2.95 (35.5%)

Cmax: µg/ml; AUC: µg*h/ml; N=3

Mean (CV%) pharmacokinetic parameters of famotidine in severe renal impairment

	Tmax (h)	Cmax	AUClast	T1/2 (h)
HZT-501	5.5 (50.6%)	103 (29.0%)	1489 (59.2%)	10.8 (35.9)
RLDs concurrent	4 (50%)	104 (19.7%)	1648 (61.2%)	11.9 (44.4%)

Cmax: ng/ml; AUC: ng*h/ml; N=3

The Cmax, AUC, and T12 of ibuprofen were similar between HZT-501 and Motrin plus Pepcid. Oral HZT-501 resulted in almost twice longer Ibuprofen Tmax than oral Motrin plus Pepcid. The pharmacokinetic parameters of famotidine were similar between HZT-501 and Motrin plus Pepcid with AUC differing to a greater extent.

A cross study comparison with the bioequivalence study, of which results are shown in section 2.2.4 and 2.2.5, revealed that severe renal impairment did not change the pharmacokinetics of

ibuprofen component but did increase all the pharmacokinetic parameters of famotidine. Its Tmax, Cmax, AUC, and half life were increased approximately 2 fold, 2 fold, 3.5 fold, and 2.5 fold, respectively.

2.3 General Biopharmaceutics

2.3.1 Is the to-be-marketed formulation identical to the one used for the phase 3 bioequivalence trial?

The to-be-marketed and phase 3 formulations are different. The sponsor addressed this formulation difference by demonstrating bioequivalence of phase 3 and commercial formulations each to the reference products.

2.3.2 What is the to-be-marketed formulation?

Commercial Formulation	
Component	Amount in Tablet (mg)
[redacted] (b) (4)	

NF = National Formulary; USP = United States Pharmacopoeia

[redacted] (b) (4)

Diagram of the [redacted] (b) (4) **Formulation of HZT-501**

(b) (4)

Components and Composition of HZT-501

(b) (4)

2.4 Analytical Section

2.4.1 What bioanalytical methods were used to assess concentration?

An LC-MS-MS method was used to quantify famotidine in human sodium heparin plasma. Ibuprofen concentration was quantified using an LC-MS-MS method. For the majority of samples, the matrix was human sodium heparin plasma. There were some human lithium heparin plasma samples.

2.4.2 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

Human sodium Heparin plasma
Famotidine
Lower Limit of Quantification (LLOQ): 1.00 ng/mL; Upper Limit of Quantification (ULOQ) : 250 ng/mL
Validated Calibration Range: 1.00 to 250 ng/mL; Linearity (Correlation of Determination, r2) : 0.9968 to 0.9996.
Inter-assay precision (%CV) ranged from 1.84% to 11.7& and accuracy (% nominal) ranged form 98% to 103%.

Ibuprofen
Lower Limit of Quantification (LLOQ): 250 ng/mL; Upper Limit of Quantification (ULOQ) : 62500 ng/mL
Validated Calibration Range: 250 to 62500 ng/mL; Linearity (Correlation of Determination, r2) : 0.9990 to 0.9996
Accuracy (% nominal) over the calibration curve concentrations ranged form 93.6% to 110%. No %CV was reported.

Human lithium Heparin plasma
Famotidine: the sponsor did not report the relevant calibration curve data for this matrix.

Ibuprofen has a r2 of 0.9984 and accuracy (% nominal) over the calibration curve concentration range of 250 ng/ml to 62500 ng/ml ranged from 93.6% to 110%.

It is concluded the assay methods of both components are acceptable. It is not expected different cations used, lithium vs sodium, could cause any significant difference in the assay precision or accuracy of LC/LC/MS for either component.

2.4.3 What are the lower and upper limits of quantification (LLOQ / ULOQ), accuracy and precision?

Human sodium Heparin plasma
Famotidine
Precision (%CV) for Quality Control Samples at Low, Medium, and High: Intra-Assay : 1.07 to 7.17%& Inter-Assay : 3.52 to 7.76%
Accuracy (% of Nominal) for Quality Control Samples at Low, Medium, and High: Intra-Assay : 89.0 to 103%& Inter-Assay : 96.0 to 101%
Precision (%CV) for LLOQ Quality Control Samples: Intra-Assay : 6.27 to 15.1% & Inter-Assay : 11.2%
Accuracy (% of Nominal) for LLOQ Quality Control Samples: Intra-Assay : 98.2 to 106% & Inter-Assay : 103%
Procedural Overall Mean Recovery\: Famotidine : 107% & Internal Standard (b) (4)

: 101%

Interference of famotidine assays by ibuprofen was determined at their respective concentrations of 125 ng/ml and 62500 ng/m, and the result showed a CV% of 1.72% and % accuracy of 96.8%. Based on the Cmax ranges of both components, the inference result supports that the assay method for famotidine is acceptable.

Since some samples were mixed with heparin lithium, the sponsor compared the precision and accuracy of analyzing quality control samples of famotidine in both matrices.
Comparison of quality control samples of famotidine in 2 different matrices.

Analyte	Human Plasma	Intra-assay Precision	Intra-assay Accuracy
Famotidine	Sodium heparin	0.472 to 2.65%	92.8 to 103%
Famotidine	Lithium heparin	0.432 to 1.56%	96.0 to 106%

Ibuprofen:
Precision (%CV) for Quality Control Samples at Low, Medium, and High: Intra-Assay: 1.35 to 9.17% & Inter-Assay : 2.65 to 7.85%
Accuracy (% of Nominal) for Quality Control Samples at Low, Medium, and High: Intra-Assay: 95.7 to 106% & Inter-Assay : 98.2 to 104%
Precision (%CV) for LLOQ Quality Control Samples: Intra-Assay: 6.71 to 13.4% & Inter-Assay : 11.4%
Accuracy (% of Nominal) for LLOQ Quality Control Samples: Intra-Assay: 88.0 to 99.6% & Inter-Assay: 94.8%
Procedural Overall Mean Recovery: Ibuprofen: 99.4% & Internal Standard (b) (4)
: 99.4%

Interference of ibuprofen assays by famotidine was determined at their respective concentrations of 31,250 ng/ml and 250 ng/m, and the result showed a CV% of 4.66% and % accuracy of 102.8%. Based on the Cmax ranges of both components, the inference result supports that the assay method for famotidine is acceptable.

Since some samples were mixed with heparin lithium, the sponsor compared the precision and accuracy of analyzing quality control samples of ibuprofenin both matrices.
Comparison of quality control samples of ibuprofen in 2 different matrices.

The assay precision and accuracy is deemed adequate for either of famotidine or ibuprofen.

Analyte	Human Plasma	Intra-assay Precision	Intra-assay Accuracy
Ibuprofen	Sodium heparin	0.540 to 5.47%	90.7 to 101%
Ibuprofen	Lithium heparin	2.98 to 6.50%	95.4 to 99.7%

In summary, the assay method developed for either ibuprofen or famotidine is deemed acceptable.

2.4.4 What is the sample stability under the conditions used in the study (long-term, freeze-thaw, sample-handling, sample transport, autosampler)?

Human lithium Heparin plasma
Stability assessment of famotidine samples
In Plasma Extract Stored at Room Temperature (approx. 24°C): Stable for at least 48 Hours

In Human Sodium Heparin Plasma Stored at Room Temperature (approx. 24°C) : Stable for at least 6 Hours
In Human Sodium Heparin Plasma Subjected to Freeze-and-Thaw Cycles: Stable after 3 Cycles
Standard Stock Solution (50.0 µg/mL in 50% MeOH) at Room Temperature (approx. 24°C): Stable for at least 12 Hours
Standard Spiking Solution (10.0 ng/mL in 50% MeOH) at Room Temperature (approx. 24°C): Stable for at least 12 Hours
Internal Standard Working Solution (b) (4), 100 ng/mL in 50% MeOH) at Room Temperature (approx. 24°C)

Stability assessment of ibuprofen samples
In Plasma Extract Stored at Room Temperature (approx. 24°C) : Stable for at least 42 Hours
In Human Sodium Heparin Plasma Stored at Room Temperature (approx. 24°C) : Stable for at least 6 Hours
In Human Sodium Heparin Plasma Subjected to Freeze-and-Thaw Cycles : Stable after 3 Cycles
Standard Stock Solution (5.0 mg/mL in MeOH) at Room Temperature (approx. 24°C): Stable for at least 13 Hours
Standard Spiking Solution (625 µg/mL in 50% MeOH) at Room Temperature (approx. 24°C): Stable for at least 13 Hours
Standard Spiking Solution (2.5 µg/mL in 50% MeOH) at Room Temperature (approx. 24°C): Stable for at least 13 Hours

Human lithium Heparin plasma
Stability assessment of famotidine samples
In Plasma Extract Stored at Room Temperature (approx. 24°C): Stable for at least 6 Hours
In Human Sodium Heparin Plasma Subjected to Freeze-and-Thaw Cycles: Stable after 3 Cycles

Stability assessment of ibuprofen samples
In Plasma Extract Stored at Room Temperature (approx. 24°C): Stable for at least 6 Hours
In Human Sodium Heparin Plasma Subjected to Freeze-and-Thaw Cycles: Stable after 3 Cycles

It is concluded that samples were handled properly with adequate stability for either component in various storage or handling procedures/conditions.

3 Comments on the proposed labeling

Section 2

The sponsor's proposed labeling statement of (b) (4) has been deleted The sponsor's proposed labeling statement of (b) (4) has been deleted by the review team because there is no information about how patients were instructed to take the proposed product and furthermore one of the phase III studies has been discounted from the overall clinical study submissions due to misconduct at the study site.

(b) (4)

Section 7.

The statement of (b) (4) Should be modified to "Co-administration of ibuprofen (800 mg) and famotidine (40 mg) increased ibuprofen Cmax by 15.6% but did not affect its AUC, and increased famotidine AUC and Cmax by 16% and 22%, respectively. "

(b) (4)

Section 8.5

The statement of (b) (4)

(b) (4)

should be modified to the following.

Famotidine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection and adjusting dosing interval, and it may be useful to monitor renal function [*see Warnings and Precautions* (b) (4)].

Section 12.3

(b) (4)

Section 12.3

The following statement under Metabolism should be deleted (b) (4)

(b) (4)

The following statement should be added to section 12.3

(b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PEIFAN J BAI
03/01/2011

SUE CHIH H LEE
03/01/2011

BIOPHARMACEUTICS REVIEW Office of New Drugs Quality Assessment			
Application No.:	Original 22-519, and Amendments (0019 and 0020)	**Reviewer: Houda Mahayni, Ph.D.**	
Submission Date:	3/23/10, 9/24/10, 10/18/10, and 2/15/11		
Division:	DGEP	**Team Leader: Angelica Dorantes, Ph.D.**	
Sponsor:	Horizon Therapeutics	**Supervisor: Patrick J. Marroum, Ph.D.**	
Trade Name:	HZT-501	**Date Assigned:**	5/8/10
Generic Name:	(Ibuprofen/ famotidine)	**Date of Review:**	12/5/10 and 2/17/11
Indication:	Reduction of the risk of development of ibuprofen-associated upper gastrointestinal ulcers in patients who require use of ibuprofen	**Type of Submission: Original New Drug Application and Amendments 0019 and 0020**	
Formulation/strengths	Tablet/(800 mg/26.6 mg)		
Route of Administration	Oral		

SUBMISSION:

HZT-501 is a fixed-dose combination, immediate-release, solid oral dosage form containing 800 mg ibuprofen and 26.6 mg famotidine. The proposed indication is for the reduction of the risk of development of ibuprofen-associated upper gastrointestinal (UGI) ulcers in patients who require use of ibuprofen.

This review will focus on assessing the dissolution method and the proposed dissolution specifications.

BIOPHARMACEUTIC INFORMATION:

The HZT-501 drug product is a (b) (4) formulation. (b) (4)

(b) (4)

The composition of the drug product is provided in Table 1.

Table 1: Components and Composition of the HZT-501 Tablet

(b) (4)

Dissolution Method Development for the HZT-501 (b) (4) **Formulation:**

Background

Both of the ibuprofen and famotidine use United States Pharmacopoeia (USP) dissolution methods, USP <711> dissolution apparatus 2 (Paddle), at a speed of 50 rpm. The famotidine monograph specifies a dissolution media of 0.1 N phosphate buffer, pH 4.5; whereas, the monograph for ibuprofen tablets specifies a dissolution media of 50 mM phosphate buffer, pH 7.2. Horizon aimed at developing a single dissolution method that measures both ibuprofen and famotidine in the HZT-501 tablet.

In the pre-New Drug Application (NDA) meeting package submitted on November 17, 2009 [Serial No. 0048], Horizon proposed using a dissolution method using USP <711> dissolution apparatus 2 (Paddle), at speed of 75 rpm, and media with pH 6.8. This method was investigated as an alternative to the dissolution method used during development, consisting of Paddle at 50 rpm and a media with pH 7.2. At the condition proposed in the pre-NDA meeting famotidine quickly went into solution (b) (4) at 30 minutes). As such, Horizon has reverted back to the method used for the finished HZT- 501 tablets during development for commercialization. This method uses USP <711> apparatus 2 (Paddle), a speed of 50 rpm, and a potassium phosphate buffer media with pH 7.2.

Evaluating the Effect of pH

When the HZT-501 (b) (4) formulation was developed, the effect of pH on the dissolution of the two actives was evaluated. Dissolution data of HZT-501 (b) (4) stability prototype lot 11011.001 were collected at pH 4.5, 5.8, 6.8, and 7.2 using USP apparatus 2 (Paddle) at 50 rpm. Results from this experiment are shown in Figure 2 and Figure 3.

Figure 2: Famotidine Release Results for (b) (4) Stability Prototype Lot 11011.001 in Different Media

(b) (4)

Figure 3: Ibuprofen Release Results for Tablet-in-Tablet Stability Prototype Lot 11011.001 in Different Media

(b) (4)

After 15 or 20 minutes, the mean famotidine release profiles remain essentially the same, regardless of the pH of the media. However, the ibuprofen profiles show an effect regarding the impact of lower pH. Dissolution at pH 6.8 and pH 7.2 are nearly identical after 30 minutes, whereas, at the low pH value, the ibuprofen has difficulty getting into solution. Based on this information, the sponsor selected the dissolution media of 50 mM phosphate buffer at pH 7.2.

Evaluating the Effect of Apparatus and Speed

Additional studies evaluated the impact of apparatus and speed on the dissolution of the tablet. Studies evaluated USP <711> apparati 1 (Basket) and 2 (Paddle). Each apparatus was evaluated at two speeds with Paddle assessed at 50 rpm and 75 rpm, and Basket at 75 rpm and 100 rpm. Testing was performed on 12 tablets of the HZT-501 commercial formulation lot F-0063-035. The studies used a dissolution media consisting of 900 mL water with 50 mM phosphate buffer at pH 6.8 (not pH 7.2, the pH selected for the proposed dissolution method).

Figure 4 and Figure 5 show plots of the mean (n=12) release results for famotidine and ibuprofen, respectively, when Paddle speed is modified. Figure 6 and Figure 7 show the mean (n=12) release results for famotidine and ibuprofen, respectively, when the Basket speed is modified.

Figure 4: Famotidine Release Profile in pH 6.8 buffer with USP Apparatus 2 (Paddle) at 50 rpm and 75 rpm

(b) (4)

Figure 5: Ibuprofen Release Profile in pH 6.8 buffer with USP Apparatus 2 (Paddle) at 50 rpm and 75 rpm

(b) (4)

Figure 6: Famotidine Release Profile in pH 6.8 buffer with USP Apparatus 1 (Basket) at 75 rpm and 100 rpm

(b) (4)

Figure 7: Ibuprofen Release Profile in pH 6.8 buffer with USP Apparatus (Basket) at 75 and 100 rpm

(b) (4)

For ibuprofen, the Paddle at both 50 rpm and 75 rpm showed a release rate that was nearly identical, with an average release (b) (4) at 10 minutes. The use of Basket appeared to produce variable results in the release of ibuprofen. The sponsor reported the relative standard deviation at 30 minutes to be (b) (4) for samples at 75 and 100 rpm in Basket, respectively. A speed of 100 rpm induced a corresponding higher release rate than 75 rpm; however, the results were slower than the Paddle, with the average release (b) (4) at 60 minutes.

For famotidine, the Paddle results showed a release rate that corresponded to the increase in Paddle speed with a higher level of variation in famotidine results at 50 rpm versus 75 rpm. With a Paddle speed of 75 rpm, the famotidine

average release rate was (b) (4) at 10 minutes. The sponsor reported the relative standard deviation (n=12) for famotidine results using Paddle at 75 rpm to be (b) (4) at 30 minutes and 60 minutes, respectively; and, the relative standard deviation (n=12) for the famotidine results to be (b) (4) at 50 rpm in 30 and 60 minutes, respectively.

Based on the available data, the sponsor selected to use a single dissolution method that measures both ibuprofen and famotidine for the HZT-501 tablet. The method selected is USP <711> Dissolution apparatus 2 (Paddle) at 50 rpm and dissolution media of 900 mL of 50 mM phosphate buffer, pH 7.2. The media and conditions are based on the USP ibuprofen tablet monograph. The USP famotidine tablet monograph uses a dissolution media with pH 4.5 (same apparatus and speed), which is not an optimal medium for ibuprofen dissolution testing.

The dissolution method parameters for HZT-501 tablet are as follows:

Dissolution Apparatus:	USP <711> Apparatus II (Paddle)
Dissolution Medium:	50 mM Potassium Phosphate Buffer, pH 7.2
Dissolution Medium Volume:	900 mL
Temperature in Vessel:	37.0º C ± 0.5° C
Speed:	50 rpm

At the development stage, the sponsor selected Q at 60 minutes. However, Horizon has lowered the time point for Q from 60 minutes to 30 minutes for both ibuprofen and famotidine, as requested by the Agency in its November 9, 2009 letter. Hence, the sponsor proposed the following dissolution specifications for HZT-501 tablet:

Q = (b) (4) at 30 minutes for ibuprofen
Q = (b) (4) at 30 minutes for famotidine

After conducting an evaluation of the NDA, FDA requested in its September 15, 2010 CMC Information Request letter for Horizon to lower the ibuprofen time point for Q to 15 minutes. On September 24, 2010, Horizon accepted to revise the ibuprofen dissolution specification to Q = (b) (4) at 15 minutes. Also, Horizon provided the revised drug product specification in the CMC amendment dated October 18, 2010.

The CMC Information Request letter dated January 14, 2011, requested Horizon to change the famotidine dissolution specification to Q (b) (4) at 30 minutes. Horizon responded on February 8, 2011 with the submission of amendment 0019 proposing to change the dissolution method and specification for famotidine in the HZT-501 tablet. On February 14, 2011, during a teleconference between FDA and Horizon, an agreement was reached for Horizon to tighten the HZT-501 tablet famotidine dissolution specification to Q = (b) (4) at 30 minutes from Q = (b) (4) at 30 minutes using the current HZT-501 tablet dissolution method described in the NDA. FDA also suggested that the dissolution testing for the (b) (4) could be removed as a regulatory requirement. Horizon submitted amendment 0020 dated February 15, 2011 in response to CMC Information Request letter dated January 14, 2011 and February 14, 2011 teleconference. In this amendment, Horizon updated Module 2 and 3 section of NDA 22-519 with the specification change for famotidine in the HZT-501 tablet. Hence, FDA and Horizon are in agreement on the following commercial dissolution specification for HZT-501 tablet:

Q = (b) (4) at 15 minutes for ibuprofen
Q = (b) (4) at 30 minutes for famotidine

Dissolution results for ten lots of HZT-501 tablets are shown in Table 2, Table 3, Table 4, and Table 5. These results were collected at the development specification of Q= (b) (4) at 60 minutes for both famotidine and ibuprofen. Therefore, the conduct of stage II testing in these lots is based on tablets not meeting the acceptance limit for famotidine (Q= (b) (4) at 60 minutes), not the commercial proposed specification (Q= (b) (4) in 30 minutes for famotidine).

Table2: Batch Analysis Results for HZT-501 Tablet Lots 11014.001 – 11014.003

Lot Number	11014.001				11014.002				11014.003			
Dissolution – Ibuprofen (%LC)	Mean	Max.	Min.	%RSD	Mean[1]	Max.	Min.	%RSD	Mean	Max.	Min.	%RSD
5 minutes												
10 minutes												
15 minutes												
30 minutes												
45 minutes												
60 minutes												
75 minutes												

(b) (4)

Lot Number	11014.001				11014.002				11014.003			
Dissolution – Famotidine (%LC)	Mean	Max.	Min.	%RSD	Mean[1]	Max.	Min.	%RSD	Mean	Max.	Min.	%RSD
5 minutes												
10 minutes												
15 minutes												
30 minutes												
45 minutes												
60 minutes												
75 minutes												

(b) (4)

[1] Dissolution testing was conducted to Stage II, n = 12 tablets

Table 3: Batch Results for the HZT-501 Tablet Lots 11014.004 – 11014.006

Lot Number	11014.004				11014.005				11014.006			
Dissolution – Ibuprofen (%LC)	Mean[1]	Max.	Min.	%RSD	Mean	Max.	Min.	%RSD	Mean	Max.	Min.	%RSD
5 minutes												
10 minutes												
15 minutes												
30 minutes												
45 minutes												
60 minutes												
75 minutes												

(b) (4)

Lot Number	11014.004				11014.005				11014.006			
Dissolution – Famotidine (%LC)	Mean[1]	Max.	Min.	%RSD	Mean	Max.	Min.	%RSD	Mean	Max.	Min.	%RSD
5 minutes												
10 minutes												
15 minutes												
30 minutes												
45 minutes												
60 minutes												
75 minutes												

(b) (4)

[1] Dissolution testing was conducted to Stage II, n = 12 tablets

Table 4: Batch Results for the HZT-501 Tablet Lots 11014.007, 11014.010, and 11014.011

Lot Number	11014.007				11014.010				11014.011			
Dissolution – Ibuprofen (%LC)	Mean	Max	Min	%RSD	Mean	Max	Min	%RSD	Mean	Max	Min	%RSD
5 minutes												
10 minutes												
15 minutes												
30 minutes												
45 minutes												
60 minutes												
75 minutes												

(b) (4)

Lot Number	11014.007				11014.010				11014.011			
Dissolution – Famotidine (%LC)	Mean	Max	Min	%RSD	Mean	Max	Min	%RSD	Mean[1]	Max	Min	%RSD
5 minutes												
10 minutes												
15 minutes												
30 minutes												
45 minutes												
60 minutes												
75 minutes												

(b) (4)

[1] Dissolution testing was conducted to Stage II, n = 12 tablets

Table 5: Batch Results for the HZT-501 Tablet Lot 11014.012

Lot Number	11014.012			
Dissolution – Ibuprofen (%LC)	Mean	Max	Min	%RSD
5 minutes	(b) (4)			
10 minutes				
15 minutes				
30 minutes				
45 minutes				
60 minutes				
75 minutes				

Lot Number	11014.012			
Dissolution – Famotidine (%LC)	Mean	Max	Min	%RSD
5 minutes	(b) (4)			
10 minutes				
15 minutes				
30 minutes				
45 minutes				
60 minutes				
75 minutes				

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Reviewer's Note:

Conducting dissolution testing for the (b) (4) is not necessary, as the dissolution method for the HZT-501 (b) (4) formulation is performed on the final dosage form, which includes dissolution testing of the (b) (4).

Dissolution Data of Phase 3 and Commercial HZT-501 Tablets:

During the Phase 3 clinical trials, Horizon determined that the Phase 3 combination tablet had suboptimal stability for commercial distribution. Therefore, Horizon developed a new (b) (4) formulation of HZT-501 for commercialization and conducted a Phase 1 bioequivalence study (Study HZ-CA-015). According to Horizon, the results of this study in 36 subjects showed that famotidine and ibuprofen in the Phase 3 combination tablet and commercial (b) (4) formulations of HZT-501 were bioequivalent as measured by Cmax, and AUC.

Horizon has provided the dissolution results in Table 8 for the HZT-501 Phase 3 combination tablet and commercial (b) (4) lots used in the bioequivalence Study HZ-CA-015. Plots of the mean values for the dissolution data for the two lots are shown in Figure 10.

Table 8: Dissolution Profiles of the Drug Product Lots used in Study HZ-CA-015

Sample Times	Famotidine (%LC)							
	Lot 11003.013 (Phase 3 Combination Tablet)				Lot 11014.004 (Commercial Formulation)			
	Mean	Max	Min.	%RSD	Mean	Max	Min.	%RSD
5 minutes	(b) (4)							
10 minutes								
15 minutes								
30 minutes								
45 minutes								
60 minutes								
75 minutes								
Sample Times	**Ibuprofen (%LC)**							
	Lot 11003.013 (Phase 3 Combination Tablet)				Lot 11014.004 (Commercial Formulation)			
	Mean	Max	Min.	%RSD	Mean	Max	Min.	%RSD
5 minutes	(b) (4)							
10 minutes								
15 minutes								
30 minutes								
45 minutes								
60 minutes								
75 minutes								

%LC = percent label claim; Max = maximum; Min = minimum; %RSD = percent relative standard deviation

Figure 10: Dissolution Profiles of the HZT-501 Tablet Lots used in Study HZ-CA-015

(b) (4)

The ibuprofen release rate for both HZT-501 formulations was rapid. At 30 and 60 minutes, both formulations have mean famotidine release values that are approximately equivalent. However, the minimum values for the famotidine release from HZT-501 commercial (b) (4) formulation are lower than in the Phase 3 combination tablet. The Phase 3 combination tablet had minimum values of (b) (4) and (b) (4) at 30 and 60 minutes, respectively, for famotidine. The HZT-501 commercial (b) (4) had minimum values of (b) (4) and (b) (4) at 30 and 60 minutes, respectively, for famotidine. The sponsor stated that this apparent slower release rate did not translate in any change in bioavailability, as the famotidine in the HZT-501 commercial (b) (4) and Phase 3 combination tablet were bioequivalent as measured by Cmax and AUC (Study HZ-CA-015 clinical study report).

RECOMMENDATION:

The following dissolution method and specifications are acceptable for HZT-501 tablet:

Dissolution Apparatus:	USP <711> Apparatus II (Paddle)
Dissolution Medium:	50 mM Potassium Phosphate Buffer, pH 7.2
Dissolution Medium Volume:	900 mL
Temperature in Vessel:	37.0º C ± 0.5° C
Speed:	50 rpm
HZT-501 Tablet Dissolution Specification:	Q = (b) (4) at 15 minutes for ibuprofen
	Q = (b) (4) at 30 minutes for famotidine

Signature	**Signature**
Houda Mahayni, Ph.D. Biopharmaceutics Reviewer Office of New Drugs Quality Assessment	Patrick J. Marroum, Ph.D. Biopharmaceutics Team Leader or Supervisor Office of New Drugs Quality Assessment
cc: ADorantes, GHolbert, TPhillips, CTran-Zwanetz	

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/s/

HOUDA MAHAYNI
02/24/2011

PATRICK J MARROUM
02/24/2011

Cover Sheet and OCP Filing/Review Form

OFFICE OF CLINICAL PHARMACOLOGY

NEW DRUG APPLICATION FILING AND REVIEW FORM

General Information About the Submission

	Information		Information
NDA Number	**NDA 22-519**	**Brand Name**	
OCP Division (I, II, III)	**III**	**Generic Name**	**Ibuprofen/famotidine**
Medical Division	**Gastroenterology**	**Drug Class**	**histamine H2-receptor antagonist /NSAID**
OCP Reviewers	**PeiFan Bai**	**Indication(s)**	**reduction of the risk of development of ibuprofen-associated, upper gastrointestinal (GI) ulcers in patients who require use of ibuprofen**
OCP Team Leader	**Sue-Chih Lee**	**Dosage Form**	**Tablets**
Date of Submission	**March 23, 2010**	**Proposed Dosing Regimen**	**Ibuprofen 800 mg/famotidine 26.6 mg**
Estimated Due Date of OCP Review	**Nov 22, 2011**	**Route of Administration**	**oral**
Medical Division Due Date		**Sponsor**	**Horizon**
PDUFA Due Date	**Jan 22, 2011**	**Priority Classification**	**Standard**

Clin. Pharm. 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**	**6**		
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) -	**X**	**1**		
1.1. *HEALTHY VOLUNTEERS-*				
single dose:	**X**	**6**		**BA, BE, food effect, DDI**
multiple dose:				
1.1.1. PATIENTS-				
single dose:				
multiple dose:	**X**	**3**		**Safety & efficacy**
Dose proportionality -				
fasting / non fasting single dose:				
fasting / non fasting multiple dose:				

Drug-drug interaction studies -	**X**	**1**		**Combination product vs individual components**
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:	**X**	**3**		**Combination product vs individual component**
Bioequivalence studies -				
traditional design; single / multi dose:	**single**	**3**		
replicate design; single / multi dose:				
Food-drug interaction studies:	**X**	**1**		**Food effect**
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**6**	**6**		**Study HZ-CA-017 (to-be-marketed formulation vs an EU ibuprofen product) will be submitted in a 4-month safety report**

Filability and QBR comments		
	"X" if yes	***Comments***
Application filable ?	**x**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to be marketed one?
Comments sent to firm	**x**	FDA letter date if applicable.
QBR questions (key issues to be considered)	• **What are the design features of the submitted studies used to support the labeling claims and fulfillment of PWR?**	

Other comments or information not included above	
Primary reviewer Signature and Date	
Secondary reviewer Signature and Date	

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22519	ORIG-1	HORIZON PHARMA INC	HZT-501

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/s/

PEIFAN J BAI
05/12/2010

SUE CHIH H LEE
05/12/2010