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APPLICATION NUMBER:

022519Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 22, 2011
From	Lynne P. Yao, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	22-519
Applicant	Horizon Therapeutics, Inc.
Date of Submission	March 23, 2010
PDUFA Goal Date	April 23, 2011
Proprietary Name / Established (USAN) names	Ibuprofen/famotidine
Dosage forms / Strength	Tablet (Ibuprofen 800 mg/famotidine 26.6 mg)
Proposed Indication(s)	1. For the reduction of the risk of development of ibuprofen-associated, upper gastrointestinal ulcers in patients who require use of ibuprofen
Recommended:	<i>Approval</i>

1. Introduction

This review examines the data submitted for a new drug application (NDA 22-519) for HZT-501, a combination of the NSAID ibuprofen (800 mg) and the histamine H₂-receptor antagonist famotidine (26.6 mg). The applicant states that HZT-501 is intended (b) (4)

The application was submitted on March 23, 2010 as a 505(b)(2) application, and was designated for standard review.

HZT-501 is manufactured using a (b) (4)

There were no substantive product quality issues uncovered by the reviewer, and all inspectional issues were resolved prior to the planned action date.

Ibuprofen (400 mg, 600 mg, and 800 mg dosage strengths) were approved for use in the US in 1974, and famotidine (40 mg) was approved in 1981. Therefore, there is a long clinical safety record for both of these products. There were no nonclinical studies provided for review in the application and the nonclinical reviewer relied on established and published information. There were no outstanding nonclinical issues noted by the reviewer.

Clinical pharmacology studies were reviewed to establish bioequivalence between the formulation of ibuprofen used in the applicant's product and the reference listed drug. The clinical pharmacology reviewer noted that the studies were complete and supported the bioequivalence of ibuprofen formulation used in HZT-501 and the reference listed drug. Additionally, clinical pharmacology studies were reviewed to establish bioequivalence of the famotidine component from the phase 3 and to-be-marketed formulations. Again, the pharmacology reviewer noted that the studies were complete and supported the bioequivalence of the famotidine formulation used in HZT-501 clinical trials and the to-be-marketed formulation. There were no outstanding clinical pharmacology issues noted by the reviewer.

Establishment of the efficacy and safety of HZT-501 relied upon two randomized, double-blind, placebo controlled trials evaluating the effect of HZT-501 in the reduction of endoscopically diagnosed upper gastrointestinal ulcers in patients who required use of ibuprofen for at least 6 months. One of the studies (study HZ-CA-301) demonstrated a statistically significant difference in the proportion of patients who developed upper gastrointestinal ulcers when using the applicant's pre-specified analysis. However, when more conservative analysis methods were used, the study failed. The second study, Study HZ-CA-303, demonstrated a highly statistically significant difference. The statistical reviewer concluded that study HZ-CA-301 failed to provide persuasive evidence of effectiveness, but study HZ-CA-303 was highly persuasive. The clinical reviewer also noted the same finding. The review will focus on the strength of the efficacy findings and how they compare to other products approved for the reduction of risk of NSAID-associated ulcers. Additionally, the

safety profile will HZT-501 will be reviewed and compared with the individual safety profiles of the previously approved drug products, ibuprofen and famotidine.

During the review cycle, the requirement for post-marketing studies triggered under the Pediatric Research Equity Act (PREA) was also reviewed. Four post-marketing studies were negotiated and are discussed in Section 13.

Overall, all of the review disciplines have recommended an approval action for this application. This memo documents my concurrence with the review teams' recommendations for an Approval action.

2. Background

A. Clinical Background

Ibuprofen is a non-steroidal anti-inflammatory drug (NSAID) that was initially approved for use in the U.S. in 1974, and subsequently approved for over-the-counter (OTC) use in 1984. Ibuprofen is indicated for the relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis; for the relief of mild to moderate pain, and for the treatment of primary dysmenorrhea. Ibuprofen is also approved for OTC use in patients ≥ 6 months of age for relief of minor aches and pains, and temporary relief of fever. The effects of ibuprofen are mediated through inhibition of cyclooxygenase (COX), the rate-limiting enzyme in prostaglandin synthesis. Prostaglandins are mediators of pain, inflammation and fever. Thus, reduction in prostaglandin synthesis by inhibition of COX by NSAIDs produces reductions in pain, inflammation, and fever.

Major complications associated with NSAID use are secondary to toxicity to the gastrointestinal (GI) tract. Although NSAIDs have been associated with GI injury from the mouth to the anus, the upper gastrointestinal tract (UGI) is the most common site for toxicity. Several products have been studied for risk reduction of NSAID-associated UGI toxicity including misoprostol, proton pump inhibitors, Histamine-2 (H₂) receptor antagonists, and selective NSAIDs (e.g., COX-2 selective drugs). The mechanisms associated with NSAID-associated adverse effects in the GI tract include: 1) decrease in duodenal mucosal bicarbonate, 2) reduction in gastric mucosal blood flow as a consequence of inhibitory effects on the biosynthesis of protective endogenous prostaglandins; 3) prevention of the increase in cell replication at ulcer margins; and 4) inhibition of platelets hemostasis (adhesion, activation, or thrombus propagation).

Clinically, these effects may result in the formation of gastric ulcers (GUs) and/or duodenal ulcers (DUs), with or without associated symptoms. In turn, ulcers may lead to serious UGI complications (UGICs) including bleeding, perforation into the peritoneal cavity, obstruction due to pre-pyloric or antral GU scarring, and penetration into adjacent solid organs. Bleeding is the most common UGIC of NSAID therapy, perforations are less common, and gastric outlet obstructions and penetrations are the least common. Although the site of NSAID-associated GI complications can be anywhere along the GI tract, the most common site is the upper gastrointestinal tract and the most common complications are upper GI bleeds from GUs and/or DUs.

Approximately 1% to 2% of NSAID users develop UGICs per year, a rate 3 to 5 times higher than non-NSAID users. The risk of severe NSAID-related UGICs is greater in patients with well-established risk factors. Thus, certain groups of NSAID users appear to be at greater risk for development of NSAID-induced ulcer complications and should, therefore, be given greater consideration for strategies to prevent or reduce ulceration. The risk factors include prior history of peptic ulcer disease (PUD) or ulcer complications, advanced age, high NSAID dose and/or long duration, as well as the use of glucocorticoids, anticoagulants, antiplatelet agents, and alcohol. The most important risk factor for an NSAID-induced complication is a history of PUD or a prior ulcer complication, factors that increase the risk for NSAID-induced GI events by 2-fold to 4-fold (Bombardier, *et al*, 2000; Silverstein, *et al*, 1995; Silverstein, *et al*, 2000; Singh and Triadafilopoulos, 1999). While some case-control studies have suggested that the risk of NSAID-associated GI complications is highest within the first 30 days of NSAID use (Gabriel *et al*, 1991, Graham and Malaty, 1999, Griffin, *et al*, 1991), other controlled prospective studies indicate that the risk of serious NSAID-induced GI complications appears to be cumulative and linear (Bombardier, *et al*, 2000; Silverstein, *et al*, 1995; Silverstein, *et al*, 2000). Concurrent use of more than one NSAID is also a risk factor because this practice essentially increases total NSAID dose, the most common example being the combined use of prescribed NSAIDs with LDA (≤ 325 mg aspirin per day) or with OTC NSAIDs.

Famotidine is an H₂-receptor antagonist (H₂-RA) and was first approved for use in the U.S. in 1981. Famotidine is indicated for the short-term treatment of active duodenal ulcers; maintenance therapy for duodenal ulcers; short-term treatment of active benign gastric ulcers; short-term treatment of gastroesophageal reflux disease; and treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, and multiple endocrine adenomas). The effects of famotidine are mediated through inhibition of histamine receptors on the parietal cells of the stomach. Competitive inhibition of H₂-receptors suppresses the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid.

Many studies have been conducted to evaluate the effect of different gastric acid-reducing therapies (PPIs and H₂-RAs) and cytoprotective agents (e.g., misoprostol) in the reduction of risk of development of NSAID-associated gastric ulcers. Indeed, misoprostol, lansoprazole, and esomeprazole have all been approved for the indication of reduction of risk of NSAID-associated gastric ulcers. Additionally, two combination PPI and NSAID products have also been approved, Napra Pac (lansoprazole/naproxen) and Vimovo (esomeprazole/naproxen). Registration endoscopy trials of PPIs to evaluate the risk reduction of NSAID-associated gastric ulcers have been 3-6 month, randomized, placebo-controlled and/or active-controlled trials in patients who required chronic use of NSAIDs. Patients had to have no evidence of ulcers on baseline upper endoscopy. Patients were treated with NSAIDs and were randomized to a PPI or placebo and underwent upper endoscopies to assess for GUs and DUs. These studies are discussed in greater detail in Section 7, Clinical/Efficacy. There have been no H₂-RAs approved for the reduction of risk of development of NSAID-associated gastric ulcers in the U.S. However, there have been several studies that have evaluated H₂-RAs for this indication published in the literature (Taha, *et al*, N Engl J Med, 1996; Taha, *et al*, Lancet, 2009). These studies concluded that famotidine (40 mg) was associated with reduction of risk of NSAID-associated gastric ulcers.

B. Regulatory Background

Presubmission Regulatory Activity

HZT-501 was developed under IND 72,116. The application was submitted on March 23, 2010 as a 505(b)(2) new drug application. The applicant referenced Pepcid for the famotidine component. For the ibuprofen component, the applicant relied on FDA's previous findings of safety and efficacy for NDA 017-463, Motrin, the innovator product. Additionally, all bioequivalence studies for the ibuprofen component of their product were compared to Ibu, the listed drug, because Motrin was discontinued. This application was reviewed by the 505(b)(2) committee and they agreed that the references in this application were correct. The application was granted a standard review. The following list includes highlights of the development of the product:

- June 13, 2005: A pre-IND meeting was held to discuss the development plan for the product. The Agency stated that adequate and well-controlled efficacy studies would be required to assess the effectiveness of HZT-501 in reduction and/or prevention of NSAID-induced ulcers.
- May 18, 2006: An end of phase 2 (EOP2) meeting was held to discuss the phase 3 clinical development program for HZT-501. The Agency recommended that the applicant conduct two 24-week clinical studies. Additionally, the Agency agreed that a statistically significant and clinically meaningful treatment effect in the cumulative incidence of endoscopically documented gastric and/or duodenal ulcers of unequivocal depth and at least 3 mm in diameter would support demonstration of efficacy of HZT-501.
- December 19, 2006: SPA agreement reached for phase 3 clinical study protocols.
- May 22, 2007: Horizon submits request to increase sample sizes for the phase 3 clinical studies.
- August 31, 2007: The agency states that any changes to the sample sizes for the phase 3 clinical studies under the SPA agreement would constitute a change in the SPA and result in a nullification of the SPA agreement.
- September 15, 2007: The applicant formally submits a protocol amendment to increase the sample size of one of the phase 3 studies, HZ-CA-303.
- October 30, 2008: The Agency recommended that both the life table analysis and crude rate analysis be performed in accordance with the treatments to which they actually received. Furthermore, the Agency clarified that “in order to claim your study drug HZT-501 is effective for the proposed indication, the results for both the life table and crude rate analyses should show positive results in favor of HZT-501 for both randomized and treated populations.”

- December 17, 2009: Pre-NDA meeting held (see meeting minutes under IND 72,116 dated January 19, 2010 and January 28, 2010 pre-NDA meeting minutes clarification). The Agency clarified that the crude rate + early termination (treated as treatment failures) analysis will be used for product labeling purposes. However, the determination of early terminations that were not treatment-related could be acceptable if the applicant was able to provide a reasonable explanation as to why these patients were not treatment related.
- March 23, 2010: NDA 22-519 submitted by the applicant.
- December 16, 2010: Additional information received from the applicant important to the review of the application received, thus triggering a Major Amendment and extending the review clock to April 22, 2011.

C. Current Submission and Review

The application was submitted on March 23, 2010. This submission was granted a standard review.

Clinical Review by A. Niak, dated April 22, 2011

Statistical Review by W.J. Chen, with concurrence by M. Welch, dated March 28, 2011 and team leader memo by M. Welch dated April 22, 2011

Pharmacology/Toxicology Review by D.C. Gautam with concurrence by S.K. Chakdar, dated December 6 and December 7, 2010

Clinical Pharmacology Review by P.F. Bai, with concurrence by S.C. Lee, dated March 1, 2011 with an addendum dated April 22, 2011

Chemistry Review by G.W. Holbert, and Manufacturing Process Review by Y. Tang, with concurrence by M.J. Rhee dated March 3, 2011 with additional memo dated April 7, 2011.

Chemistry Biopharmaceutics Review by H. Mahayni, with concurrence by P.J. Marroum, dated February 24, 2011

Division of Scientific Investigation Summary by K. Malek, dated April 8, 2011

Division of Medication Error Prevention and Analysis (DMEPA) Proprietary Name Review by Y. Maslov, with concurrence by Z. Oleszczuk, dated March 9, 2011

Pediatric and Maternal Health Staff consultation by A. Karesh, dated December 14, 2010

OSE consult by Patty Greene, dated October 18, 2010.

DRISK consult by Latonia Ford, dated March 23, 2011

3. CMC/Device

The reader is referred to the Chemistry Review by G. Holbert, and the Manufacturing Process Review by Y. Tang, dated March 3, 2011 for complete information.

General product quality considerations

HZT-501 is an immediate release (b) (4) combination product that contains ibuprofen, USP (800 mg) and famotidine USP (26.6 mg), and is supplied as a tablet for oral administration. The inactive ingredients include microcrystalline cellulose, anhydrous lactose, croscarmellose sodium, colloidal silicon dioxide, magnesium stearate, purified water, povidone, titanium dioxide, polyethylene glycol, polysorbate 80, polyvinyl alcohol, talc,

FD&C Blue #2/Indigo Carmine Aluminum Lake and FD&C Blue #1/Brilliant Blue FDF Aluminum Lake. With the exception of the colorants all excipients are of compendial grade. The colorants meet applicable FDA requirements. HZT-501 tablets are made by (b) (4)

Figure 1: HZT-501 tablet structure



(copied from Chemistry review by G. Holbert)

Drug Substance

The famotidine drug substance is manufactured by (b) (4) (DMF (b) (4)). The information submitted by the applicant concerning the famotidine drug substance was reviewed and the chemistry reviewer concluded that the information was adequate to support the identity, strength, quality, and purity of the drug product.

The ibuprofen drug substance is manufactured by (b) (4). The applicant provided references to two Type II DMF numbers (DMF (b) (4) and DMF (b) (4)), (b) (4). The information submitted by the applicant concerning the ibuprofen drug substance was reviewed and the chemistry reviewer concluded that the information was adequate to support the identity, strength, quality, and purity of the drug product.

Drug Product Manufacturing Process

The manufacture of the (b) (4)

- (b) (4)

- [REDACTED]
- [REDACTED]
- [REDACTED]
- [REDACTED]

(b) (4)

The chemistry reviewer concluded that the corrective actions taken resulted in process controls that consistently and reliably rejected defective tablets.

There were no other substantive issues noted by the chemistry reviewer and the reviewer concluded that the application provided sufficient information to assure the identity, strength, purity, and quality of the drug product.

Facilities review/inspection

A prior approval inspection was conducted at Pharmaceuticals International Inc (Pii) from November 29 to December 7. Based on the inspection a Form 483 was issued that included the following deficiencies:

1. There is no continuous performance verification or qualification program, including adjustment and suitability test after cleaning and equipment maintenance, to ensure that

(b) (4)

[REDACTED]

2. There is no consistent test method to examine Ibuprofen/Famotidine 800 mg/26.6 mg tablets to ensure that

(b) (4)

[REDACTED] Specifically, Master Batch Record for Ibuprofen/Famotidine Tablets, 800 mg/26.6 mg approved 10/14/10 requires operators to

[REDACTED]

(b) (4)

(b) (4)

3. Complaint Investigation Report CMP 10-032 was initiated on 07/22/10 in response (b) (4) from Ibuprofen/Famotidine 800 mg/26.6 mg Tablets lot 11014.010 The investigation did not adequately review the batch record which documents a (b) (4)

(b) (4)

There is evidence that tablets were damaged

(b) (4)

(b) (4)

4. Laboratory investigation IR10-019 was initiated on 11/16/2010 in response to a dissolution failure ((b) (4) against a (b) (4) specification at 30 minute for Famotidine) and an out of trend stirring time for assay and content uniformity testing for Ibuprofen/Famotidine 800 mg/26.6 mg Tablets lot 11014.011. The investigation concluded that no assignable root cause was found. The investigation did not adequately review the associated batch record which documents that (b) (4)

(b) (4)

These deficiencies led to the classification of the Pii facility as Official Action Indicated (OAI). Based on this classification the Office of Compliance recommended a withhold approval action. However, these deficiencies have subsequently been adequately addressed by the facility, and the Office of Compliance changed the classification of this facility to voluntary action indicated (VAI) and recommended an approval action for this NDA.

Conclusions and Recommendations

The chemistry reviewer noted that the application provided sufficient information to assure the identity, strength, purity, and quality of the drug product. Additionally, the chemistry reviewer added a final recommendation for an approval action on April 7, 2011, because all manufacturing deficiencies were adequately addressed by the applicant.

4. Nonclinical Pharmacology/Toxicology

The reader is referred to the Pharmacology/Toxicology Review by D. Gautam, dated December 6, 2010 for complete information.

This NDA is submitted under section 505(b) (2) of the Federal Food, Drug and Cosmetic Act and relies on studies that were not conducted by or for the applicant and for which this applicant does not have right of reference. Specifically, this NDA is supported by reference to the Agency's previous findings of safety and publicly available information on the toxicology of ibuprofen and famotidine. In addition, the applicant provided published literature to support the nonclinical safety of ibuprofen and famotidine. Toxicology studies conducted by the innovators have established the safety of ibuprofen and famotidine; no toxicology studies were conducted by the applicant.

The application included published literature for safety pharmacology/toxicology studies that were reviewed:

1. Acute single dose toxicity studies for ibuprofen in mice, rats, and dogs
2. Repeat dose oral toxicity studies (30-day and 13-week, and 26-week) for ibuprofen in rats
3. Repeat dose oral toxicity studies (30-day, and 26-week) for ibuprofen in dogs
4. Repeat dose oral toxicity studies (13-week, 26-week, and 1-year) for famotidine in rats
5. Repeat dose oral toxicity studies (30-day, 13-week, and 1-year) for famotidine in dogs
6. One 39-week, repeat dose study in cynomolgus monkeys
7. In Vitro Reverse Mutation Assay (Ames) testing for ibuprofen and famotidine
8. In Vitro Chromosomal Aberration Assays in Mammalian Cells for famotidine
9. Non-GLP 2-year carcinogenicity study for ibuprofen and famotidine in mice
10. One Segment I fertility and early embryonic development study for ibuprofen and famotidine in rats
11. One Segment II teratology study for famotidine in rats and rabbits

Acute and chronic oral toxicity studies for ibuprofen indicated that the gastrointestinal system was the most common target organ of toxicity for ibuprofen. These findings included fecal blood loss, erosions of the gastric antrum and pylorus, emesis, scouring, and albuminuria. Chronic oral toxicity studies for famotidine indicated minimal toxicological effects. There was no overt toxicity seen in rats and dogs treated with oral famotidine at doses up to 2000 mg/kg twice daily for up to 13 weeks.

Mutagenicity potential was assessed for both ibuprofen and famotidine using the Ames test. However, ibuprofen was positive in the mice chromosomal aberration assay. A non-GLP 2-year carcinogenicity study in mice was performed that concluded that ibuprofen did not have carcinogenic potential. However, the reviewer noted that these studies were not complete because the duration of study was inadequate, only a single dose level was used, and an inadequate number of animals were studied. However, the weight of the collected human safety experience with ibuprofen over the last 30 years outweighs the need for a carcinogenicity study based on the opinion of the nonclinical reviewer. A carcinogenicity

study for famotidine was reviewed and the reviewer found no evidence of carcinogenic potential for famotidine.

Reproductive toxicity and teratogenicity studies were conducted for both ibuprofen and famotidine. Reproductive toxicity for ibuprofen in rats included dystocia, delayed parturition, and decreased pup survival. Teratogenicity studies for both ibuprofen and famotidine were negative.

Conclusions and Recommendations

The pharmacotoxicology of the component drug products of HZT-501 (ibuprofen and famotidine) have been well characterized previously and the applicant has relied on this previously obtained information in this 505(b)(2) application. The pharmacology toxicology reviewer did not uncover any new safety concerns from the review of the information submitted in the application. Furthermore, the existing safety data in humans and animals for each component of HZT-501 do not suggest any serious or new safety concerns. Therefore, the clinical reviewer recommended that an approval action be taken for HZT-501. Specific labeling recommendations for Sections 8 Use in Special Populations and Section 13 Nonclinical Toxicology are detailed in section 12 below and in the clinical pharmacology review.

5. Clinical Pharmacology/Biopharmaceutics

The reader is referred to the Clinical Pharmacology Review by P.F. Bai, dated March 1, 2011 for complete information. The reviewer noted that all clinical pharmacology studies were conducted according to agreements reached with the Agency and therefore, all clinical pharmacology studies were considered adequately designed.

General clinical pharmacology/Biopharmaceutics

All bioequivalence studies were conducted as single dose studies.

Bioequivalence studies

HZT-501 is a combination product, incorporating famotidine and ibuprofen into a single tablet for oral administration. The efficacy of famotidine in reducing the risk of NSAID-associated gastric ulcers was evaluated in a phase 3 trial that was included in the application. However, the efficacy of ibuprofen relies on previously established claims of efficacy for Motrin/Ibu based on bioequivalence of the applicant's formulation of ibuprofen (HZT-405) to the comparator. Therefore, the following bioequivalence studies were performed and reviewed in this application:

1. Bioequivalence of HZT-405 to the listed drug, Ibu
2. Bioequivalence of ibuprofen component of the phase 3 formulation (HZT-501) to the commercial formulation of ibuprofen (Ibu)
3. Bioequivalence of the ibuprofen component of the commercial formulation (HZT-501 (b) (4)) to the listed drug, Ibu
4. Bioequivalence of the ibuprofen component of the phase 3 formulation (HZT-501) to the ibuprofen component of the commercial formulation (HZT-501 (b) (4))

5. Bioequivalence of famotidine component of the phase 3 formulation (HZT-501) to the famotidine component of the commercial formulation (HZT-501 (b) (4))

It should be noted that no bioequivalence studies between famotidine given at 26.6 mg, tid (the proposed dose of famotidine for HZT-501, the product in this NDA) compared to a previously approved dose of famotidine, 40 mg, bid, because clinical efficacy and safety data for the new famotidine dosing regimen were included in the current NDA. However, scientific evidence to demonstrate the relationship between the referenced product (Pepcid table, 40 mg) to the famotidine component (26.6 mg) of the proposed product was required to support the reliance of previous nonclinical safety information for the proposed product. Study HZ-CA-001 was a single dose drug-drug interaction study that evaluated the pharmacokinetic profile of the referenced product, Pepcid, 40 mg tablet. Data from this single dose study were compared to data from Study HZ-CA-016, a food-drug interaction study that evaluated the commercial formulation of the proposed product (famotidine, 26.6mg). The clinical pharmacologist estimated the multiple dose steady-state famotidine exposure (C_{max} and AUC) of the proposed product and demonstrated that the exposure was lower than that following a single dose of Pepcid, 40 mg. Therefore, these studies provide adequate scientific evidence bridging the proposed product to the listed drug, Pepcid tablets (famotidine).

Bioequivalence between applicant's ibuprofen comparator (ibuprofen 800mg, named "HZT-405" by the applicant) and the listed product (Ibu) was evaluated with a randomized, 2-period, crossover, open-label study. Twenty-two healthy subjects enrolled and completed the study. The results of the comparison of PK parameters are listed below in table 1 and table 2:

Table 1: PK 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

HZT-405 is the name given by the applicant to ibuprofen 800 mg tablet used by the applicant during phase 3 trials (this was not a new formulation of ibuprofen, however) (copied from clinical pharmacology review by P.F. Bai)

Table 2: 90% CI of ratios of the computed PK parameters for Ibuprofen following single dose oral administration

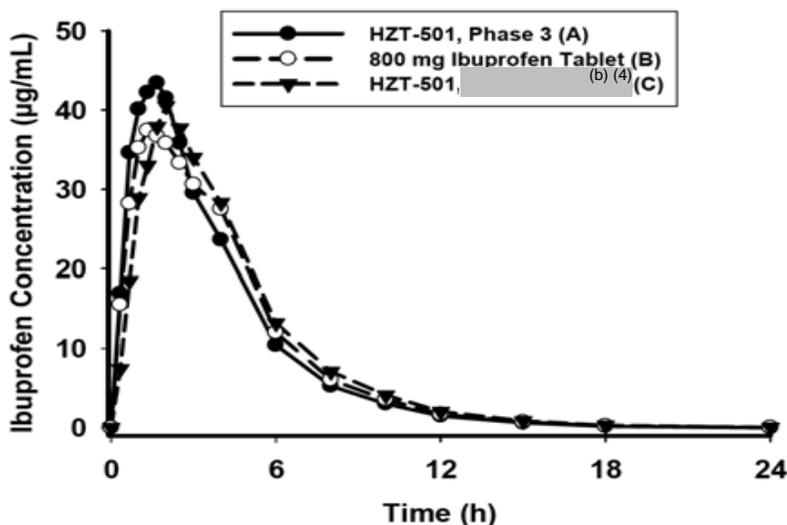
Parameter	Ratio¹	Lower Limit	Upper Limit
C _{max} (µg/mL)	107.1	100.4	114.3
AUC (µg•hr/mL)	102.1	98.0	106.4

(copied from clinical pharmacology review by P.F. Bai)

These data demonstrate that the applicant’s comparator product (HZT-405) PK parameters were bioequivalent to the PK parameters of the listed product (Ibu) as the Cmax and AUC fall within the bioequivalence acceptance range of 80-125%. The clinical pharmacology review concluded that the two products were bioequivalent.

Additionally, evaluation of the bioequivalence of the phase 3, commercial, and reference product was also performed. Thirty-six healthy subjects were enrolled and 33 subjects completed the study (see figure 2).

Figure 2: Mean plasma concentrations of three ibuprofen formulations versus time



A phase 3 product; B reference product; C commercial formulation (copied from clinical pharmacology review by P.F. Bai)

The clinical pharmacology reviewer noted that both the commercial formulation (HZT-501 (b) (4)) and the phase 3 formulation (HZT-501) were both bioequivalent to the reference product (Ibu). However, the phase 3 formulation (HZT-501) was not bioequivalent to the commercial formulation (HZT-501 (b) (4)); but no clinical efficacy studies were conducted with the ibuprofen component, therefore, the clinical pharmacologist noted that the important comparison is between the phase 3 (HZT-501) and commercial formations (HZT-501 (b) (4)) with the listed product (Ibu). Therefore, the clinical pharmacologist concluded that the criteria for ibuprofen bioequivalence were met based on the data from these studies.

Additionally, bioequivalence between the phase 3 formulation (HZT-501) and the commercial formulation (HZT-501 (b) (4)) of famotidine was also studied. The results of the PK parameters for these two formulations of famotidine are listed below in Table 3.

Table 3: PK parameters and ratios of computed PK parameters for famotidine

	HZT-501 Phase 3 Formulation Mean (\pm SD)	HZT-501 Formulation Mean (\pm SD) ^{(b) (4)}	Ratio C / A ¹ (90% CI) %
n	35	34	
T_{max} (h)	2.21 (\pm 0.779)	1.99 (\pm 0.721)	--
C_{max} (ng/mL)	57.8 (\pm 18.1)	60.6 (\pm 22.5)	103.7 (95.8, 112.3)
AUC_{0-last} (ng-h/mL)	374 (\pm 131)	387 (\pm 150)	103.6 (96.9, 110.9)
AUC_{0-inf} (ng-h/ml)	385 (\pm 135)	397 (\pm 155)	103.3 (96.7, 110.4)
t_{1/2} (h)	4.34 (\pm 1.11)	4.05 (\pm 0.958)	--

(copied from clinical pharmacology review by P.F. Bai)

These data demonstrate that the phase 3 PK parameters were bioequivalent to the PK parameters of the commercial formulation as the C_{max} and AUC fall within the bioequivalence acceptance range of 80-125%. The clinical pharmacology review concluded that the two famotidine formulations were bioequivalent. Again, as stated above, it should be noted that no bioequivalence studies between famotidine given at 26.6 mg, tid (the proposed dose of famotidine for HZT-501, the product in this NDA) compared to a previously approved dose of famotidine, 40 mg, bid, because clinical efficacy and safety data for the new famotidine dosing regimen were included in the current NDA.

Drug-drug interactions

An evaluation of a potential interaction between famotidine and ibuprofen was also required because HZT-501 is a new combination product consisting of these two drug products. A drug interaction study was conducted in a randomized, crossover, open-label study of six healthy adult male subjects. The study was conducted using Motrin and Pepcid, not the company's formulations for these products. The results of this study are shown below in table 4.

Table 4: PK parameters for ibuprofen (800 mg) and famotidine (40 mg) interaction study

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

* ng/mL for famotidine; μ g/mL for ibuprofen

** ng-h/mL for famotidine; μ g-h/mL for ibuprofen

(copied from clinical pharmacology review by P.F. Bai)

Compared to administration of either drug product alone, co-administration of these two drug products produced a slight reduction in T_{max}. However, the AUC and C_{max} for famotidine increased by 16% and 22%, respectively when given together, but these differences were not statistically significant because of the wide standard deviation. The clinical pharmacology

reviewer concluded that there was no significant pharmacokinetic interaction between ibuprofen and famotidine. The clinical pharmacology team noted that this difference in C_{max} was largely driven by one subject, and that any differences in C_{max} are likely secondary to differences in absorption that would not have a substantive influence on AUC. Furthermore, the dose of famotidine used in this study, 40 mg, is 1.5 times higher than the dose of famotidine, 26.6 mg in HZT-501. Therefore, these drug-drug interactions represent the “worst case” for a famotidine effect on ibuprofen. Thus, any effect of the famotidine on ibuprofen exposure would likely be less than what is seen in this study. For these reasons, the clinical pharmacology team concluded that there was no substantive drug-drug interaction between ibuprofen and famotidine, and that additional single dose or repeat doses were not warranted.

Pathway of elimination

The clinical pharmacology reviewer noted that ibuprofen is eliminated following metabolism to glucuronide conjugates. These metabolites are excreted in the urine. Therefore, little or no ibuprofen is eliminated unchanged and renal impairment is not likely to have an effect on ibuprofen elimination.

Famotidine is eliminated by both renal (65-70%) and metabolic routes (30-35%). Renal clearance of famotidine is higher than glomerular filtration rate and therefore it is likely that some drug is cleared by tubular secretion. Thus, it is recommended that patients with moderate or severe renal insufficiency undergo dose adjustment of famotidine either by reducing the dose or increasing the dosing interval.

Demographic interactions/intrinsic factors, special populations

Famotidine is eliminated through the kidneys (as described above), and a study in five patients with renal insufficiency (estimated GFR 20.41-40.43 mL/min) demonstrated an increased T_{max}, C_{max}, AUC and half life for the famotidine component of HZT-501. Therefore, the clinical reviewer concluded that HZT-501 is not recommended in patients with advanced renal disease. The C_{max} famotidine did not differ substantively between HZT-501 and Pepcid suspension (C_{max} of famotidine for HZT-501 was 110 ± 44.9 ng/mL compared to 101 ± 40.1 ng/mL for Pepcid suspension). The AUC for famotidine also did not differ substantively between HZT-501 and Pepcid suspension (AUC of famotidine for HZT-501 was 1674 ± 689 µg*hr/mL compared to 1790 ± 951 µg*hr/mL for Pepcid suspension). This study provides a direct bridge from the commercially available Pepcid to the applicant’s product and therefore

Other issues: food effect

The effect of food (high fat meal) on the PK parameters of both the famotidine and ibuprofen components of HZT-501 (commercial product) was evaluated in a randomized, open-label, two-period, crossover study. Twenty-eight patients were enrolled and 26 patients completed the study. The results of the study are shown below in tables 5 and 6.

Table 5: PK parameters and ratios of computed PK parameters for famotidine in fed and fasted states

	HZT-501 Fasted Mean (\pm SD)	HZT-501 Fed Mean (\pm SD)	Ratio B / A¹ (90% CI) %
n	27	27	
T_{max} (h)	2.02 \pm 0.835	2.97 \pm 1.07	--
C_{max} (ng/mL)	68.6 \pm 29.3	58.1 \pm 21.1	87.6 (77.9, 98.5)
AUC_{0-last} (ng-h/mL)	429 \pm 190	381 \pm 122	92.4 (83.2, 102.6)
AUC_{0-inf} (ng-h/mL)	439 \pm 192	392 \pm 121	92.8 (83.6, 103.0)
t_{1/2} (h)	4.41 \pm 1.22	4.23 \pm 1.26	--

Table 6: PK parameters and ratios of computed PK parameters for ibuprofen in fed and fasted states

	HZT-501 Fasted Mean (\pm SD)	HZT-501 Fed Mean (\pm SD)	Ratio B / A¹ (90% CI) %
n	27	27	
T_{max} (h)	2.05 \pm 0.674	1.80 \pm 0.924	--
C_{max} (μg/mL)	39.8 \pm 6.48	38.5 \pm 7.55	96.0 (89.0, 103.5)
AUC_{0-last} (μg-h/mL)	182 \pm 44.3	156 \pm 40.2	85.4 (81.4, 89.7)
AUC_{0-inf} (μg-h/mL)	184 \pm 44.5	157 \pm 40.3	85.4 (81.3, 89.6)
t_{1/2} (h)	2.16 \pm 0.449	2.00 \pm 0.435	--

(copied from clinical pharmacology review by P.F. Bai)

These results demonstrate that the effect of a high fat meal did not cause the famotidine AUC or the ibuprofen AUC and C_{max} to deviate out of the 80-125% bioequivalence acceptance range. However, the famotidine C_{max} failed to remain in the bioequivalence acceptance range. The clinical pharmacology reviewer also cited published literature for famotidine that described a slightly increased bioavailability by food and that the bioavailability of ibuprofen was not impacted by food (J. Clin. Pharmacol. 1992 Dec; 32(12):1110-1114). However, the clinical pharmacology reviewer noted that different formulations of these drug products could play a role in differences of the effect of food on PK parameters. It should be noted that in the phase 3 trials for the product, there were no specific instructions given to patients about dosing with or without food. The clinical pharmacology reviewer concluded that intake of a high fat diet does not appear to affect the PK parameters of HZT-501. However, the reviewer also noted that the clinical review team recommended that this information not be included in labeling because it is inconsistent with current labeling recommendation for ibuprofen that it should be taken with food if GI upset occurs when taken on an empty stomach. However, the

clinical review team agreed that the food effect information could be included in Section 12 (clinical pharmacology) of product labeling.

Conclusions and Recommendations

The clinical pharmacology reviewer concluded that the bioequivalence studies established that both the ibuprofen component and the famotidine component of the commercial product are bioequivalent to their respective reference products. Furthermore, the reviewer concluded that there was no significant drug-drug interaction between the two components of the HZT-501 when given together. Therefore, the clinical reviewer recommended that an approval action be taken for HZT-501. Specific labeling recommendations are detailed in section 12 below and in the clinical pharmacology review.

6. Clinical Microbiology

Clinical microbiology considerations do not apply to this application because HZT-501 is not intended as an antimicrobial product.

7. Clinical/Statistical- Efficacy

The reader is referred to the clinical review by A. Niak, dated April 22, 2011, and the statistical review by W.J. Chen, dated March 28, 2011 for complete information.

The data submitted to support the efficacy of HZT-501 were contained in two phase 3 trials, HZ-CA-301 and HZ-CA-303. Both studies were designed to evaluate the reduction in risk of developing ibuprofen-associated gastrointestinal ulcers, and both studies used the same fixed dose combination of ibuprofen (800 mg) and famotidine (26.6 mg) given three times daily. There were no clinical trials to assess the efficacy of ibuprofen for any clinical indications. Efficacy of ibuprofen was established based on bioequivalence to an approved formulation of ibuprofen (IBU; see section 5 clinical pharmacology/biopharmaceutics).

Both studies were randomized, double-blind, parallel-group, multicenter trials of 26 weeks duration. All of the study sites were located within the U.S.

Study designs

Study HZ-CA-301

Study HZ-CA-301 (which will be referred to as Study 301) was a multicenter, randomized, double-blind, parallel-dose study in adult patients. The study was designed to evaluate the efficacy of HZT-501 in reducing the proportion of patients who developed at least one endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer (of unequivocal depth and at least 3 mm in diameter) during a 24-week treatment period as compared to ibuprofen, in patients at risk for non-steroidal anti-inflammatory drug (NSAID)-induced ulcers.

Eligibility, treatment and assessments

Patients must be between 40 and 80 years of age, and had not used NSAIDs within the 30 days prior to study entry and who were expected to require daily administration of an NSAID for at least the coming 6 months for conditions such as the following: osteoarthritis, rheumatoid arthritis, chronic low back pain, chronic regional pain syndrome, and chronic soft tissue pain. Patients were randomly assigned in a 2:1 ratio to receive either HZT-501 or ibuprofen for 24 consecutive weeks, or until the patient developed either an endoscopically-diagnosed upper gastrointestinal ulcer and/or terminated early for other reasons. Additionally, randomization was stratified based on the following two risk factors for ulcer development; concomitant use of low-dose aspirin and/or other anticoagulant medication or history of upper gastrointestinal ulcer. Patients who had a prior history of serious GI complications (i.e., bleeding, perforation or obstruction) associated with NSAID use or primary peptic ulcer disease, erosive esophagitis, five or more erosions observed on endoscopy at screening, or creatinine clearance < 45 ml/min were excluded from the study. Patients with a document current history of H. pylori infection were also excluded from the study. However, patients with a prior history of H. pylori infection were eligible for study participation after “adequate treatment and provision of a current negative test result.”

Patients received either HZT-501 (ibuprofen 800 mg/famotidine 26.6 mg) or ibuprofen (800 mg) orally, three times a day for up to 24 consecutive weeks. Patients were prohibited from taking any NSAIDs other than study drug, and were prohibited from taking aspirin except for low-dose aspirin taken for cardiovascular prophylaxis, during the 24-week treatment period. Patients were prohibited from taking any drugs or interventions that neutralize gastric acid for more than three days during any two-week period during the 24-week treatment period. Patients were prohibited from taking any H₂-receptor antagonists and/or any proton pump inhibitors other than study drug during the 24-week treatment period. Patients taking low dose aspirin and/or other anticoagulant medication could continue to use these medications, on their usual regimen, during the treatment period.

Endoscopic examinations were performed during screening (baseline) and at weeks 8, 16, and 24, with a four-day window prior to the actual clinic visit day. Patients were deemed a treatment failure and terminated early from the study in the event they developed an endoscopically-diagnosed upper gastrointestinal ulcer of unequivocal depth and at least 3 mm in diameter. Patients who terminated early for reasons other than development of an endoscopically-diagnosed upper gastrointestinal ulcer underwent an endoscopic examination at a termination visit that was conducted as soon as possible after administration of their final dose of the study medication.

Endpoints

The primary efficacy endpoint for study 301 was:

- The proportion of subjects who developed at least one endoscopically diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week treatment period.

The secondary efficacy endpoints for study 301 were:

- The proportion of subjects who developed at least one endoscopically-diagnosed gastric ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week treatment period.
- The proportion of subjects who developed at least one endoscopically-diagnosed duodenal ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week treatment period.
- The incidence rate of NSAID-associated serious gastrointestinal complications (perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding) during the 24 week treatment period.

Study HZ-CA-303

Study HZ-CA-303 (which will be referred to as Study 303) was also a multicenter, randomized, double-blind, parallel-dose study in adult patients. The study was designed to evaluate the efficacy of HZT-501 in reducing the proportion of patients who developed at least one endoscopically-diagnosed gastric ulcer (of unequivocal depth and at least 3 mm in diameter) during a 24-week treatment period as compared to ibuprofen, in patients at risk for non-steroidal anti-inflammatory drug (NSAID)-induced ulcers.

Eligibility, treatment and assessments

The eligibility, treatments, and assessments for study 303 were identical to those of study 301.

Endpoints

The primary endpoint of study 303 was:

- The proportion of subjects who developed at least one endoscopically-diagnosed gastric ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week treatment period.

Secondary endpoints of study 303 were:

- The proportion of subjects who developed at least one endoscopically-diagnosed upper gastrointestinal (i.e., gastric and/or duodenal) ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week treatment period.
- The proportion of subjects who developed at least one endoscopically-diagnosed duodenal ulcer of unequivocal depth and at least 3 mm in diameter during the 24-week treatment period.
- The incidence rate of NSAID-associated serious gastrointestinal complications (perforation of ulcers, gastric outlet obstruction due to ulcers, gastrointestinal bleeding) during the 24 week treatment period.

Results

Study 301

There were 627 patients randomized into the study (safety population); 415 patients into the HZT-501 group and 212 patients in the Ibuprofen group. All analyses by the clinical reviewer were performed on the applicant's modified intent to treat (MITT) population (only patients who had undergone at least one study-mandated follow up EGD). The MITT population included 588 patients; 390 patients in the HZT-501 group, and 198 patients in the ibuprofen group. The applicant performed analyses on their primary population, defined as patients who had at least one follow up EGD between weeks 6.7 and 26.7. The primary population included 570 patients; 380 patients in the HZT-501 group and 190 patients in the ibuprofen group. It should be noted that the difference between the MITT and primary population in study 301 includes 18 patients who did not receive at least one endoscopy during the pre-defined study window (week 6.7 to week 26.7). Of these 18 patients, 2 patients in the MITT who were not counted in the primary population developed gastric ulcers (both patients were randomized to the HZT-501 group). However, because the MITT provides a more "inclusive" and conservative analysis of the efficacy results, the clinical reviewer used the MITT for all independent efficacy analyses. However, the statistical reviewer used the primary population for all analyses because this was the population that the applicant had pre-specified as the analysis population. I agree with the clinical reviewer's choice to evaluate the efficacy data using the MITT population. However, the different analyses chosen by the clinical and statistical reviewer did not result in any substantive differences in efficacy analyses for either study 301 or study 303. Additionally, the statistical team leader memo commented on the analysis population used. He noted that, in fact, the Agency's usual preference for the primary analysis population has been the true intent to treat population (i.e., all randomized patient who received at least one dose of study drug). However, the statistical team leader noted that from a statistical view, the randomization would likely be preserved using the true ITT, and it is my opinion that the patients excluded by using other analysis population would not necessarily have been informative.

Patients enrolled in study 301 were predominantly white (82.6%), less than 65 years of age (82.1%), and female (67.6%). There were no significant imbalances in demographic information between treatment groups.

Overall, 394 patients (62.8%) completed the study; more patients in the ibuprofen group terminated the study early (42.5%) compared to the HZT-501 group (34.5%). The applicant reported that reasons for early termination included adverse events, patient withdrawal of consent, protocol violations, patients lost to follow-up, discretion of the investigator/sponsor, endoscopically diagnosed upper GI ulcer, or patient required excluded medication (see table 7). The applicant reported that there were no statistically significant differences in the reasons for early termination between the groups; however, based on the design of the study, it would be expected that there would be a substantially higher early termination rate in the ibuprofen group due to the development of ulcers and/or adverse events related to the development of ulcers. In fact, the difference due to development of ulcers was different between the groups. However, the overall drop out rate for the HZT-501 was otherwise higher than expected. There was only an 8% difference in the drop out rate between HZT-501 and ibuprofen. For this reason, it would be reasonable to count early terminated patients as having failed the study

which would be the more conservative analysis. The most conservative analysis has been the standard approach by the statistical review team when evaluating studies of this design. The pre-specified plan to count early terminated patients as treatment successes would only be acceptable, and considered the most conservative analysis, if as expected, the drop out rate in the ibuprofen treatment group were actually much higher. As described below, this was the case for study 303.

Table 7: Patient disposition for study 301 (safety population)

	HZT-501 % (n)	Ibuprofen % (n)	Total % (n)
All Patients			
Number of Patients	66.1 (415)	33.8 (212)	100.0 (627)
Completed Study	65.5 (272)	57.5 (122)	62.8 (394)
Early Termination	34.5 (143)	42.5 (90)	37.2 (233)
Reasons for Early Termination			
Death	0.0 (0)	0.0 (0)	0.0 (0)
Adverse Events	5.8 (24)	7.1 (15)	6.2 (39)
Patient Withdrawing Consent	10.4 (43)	12.3 (26)	11.0 (69)
Protocol Violations	1.2 (5)	0.0 (0)	0.8 (5)
Patient Lost to Follow-up	5.3 (22)	2.4 (5)	4.3 (27)
Discretion of Investigator/Sponsor	2.4 (10)	4.2 (9)	3.0 (19)
Endoscopically-Diagnosed UGI Ulcer	8.0 (33)	16.0 (34)	10.7 (67)
Patient Required Excluded Medication	0.2 (1)	0.5 (1)	0.3 (2)
Other	1.2 (5)	0.0 (0)	0.8 (5)

(copied from clinical review by A. Niak)

Additionally, patient disposition information did not change substantively for most categories if evaluating the primary population; however the number and percent of patients that discontinued due to adverse event in the HZT-501 group did decrease by nine patients (5.8% to 3.9%) when evaluating the primary population (see Table 8).

Table 8: Patient disposition for the primary population (Study 301)

	HZT-501 % (n)	Ibuprofen % (n)	Total % (n)
All Pts.			
Number of Patients	66.7 (380)	33.3 (190)	100.0 (570)
Completed Study	71.6 (272)	64.2 (122)	69.1 (394)
Early Termination	28.4 (108)	35.8 (68)	30.9 (176)
Reasons for Early Termination			
Death	0.0 (0)	0.0 (0)	0.0 (0)
Adverse Events	3.9 (15)	3.7 (7)	3.9 (22)
Patient Withdrawing Consent	8.2 (31)	8.4 (16)	8.2 (47)
Protocol Violations	1.1 (4)	0.0 (0)	0.7 (4)
Patient Lost to Follow-up	3.4 (13)	1.6 (3)	2.8 (16)
Discretion of Investigator/Sponsor	2.1 (8)	3.7 (7)	2.6 (15)
Endoscopically-Diagnosed UGI Ulcer	8.4 (32)	17.9 (34)	11.6 (66)
Patient Required Excluded Medication	0.3 (1)	0.5 (1)	0.4 (2)
Other	1.1 (4)	0.0 (0)	0.7 (4)

(copied from clinical review by A. Niak)

It should be noted that differences in the criteria used to define treatment failures impacts the efficacy results substantially. As noted above, differences are noted in the reasons for early termination between the entire study population (safety population) and the primary population (the pre-specified population for all efficacy analyses by the application). The most conservative approach to the analysis of results as discussed with the statistical reviewer was to include all early terminations as treatment failures because of the small difference in drop out rates between HZT-501 and ibuprofen. The most conservative approach was also used for the statistical review for Vimovo, a recently (2010) approved NSAID (naproxen) and proton pump inhibitor (esomeprazole). Additionally, in an information request sent to the applicant in October 5, 2010, the statistical and clinical reviewers requested that additional analyses be performed in the primary population and MITT to evaluate efficacy results when all patients who terminated early were counted as treatment failures as well as an analyses of efficacy when patients with any of the following reasons for early termination were counted as treatment failures: Adverse Events, Lost to Follow-Up, early terminated by Investigator or Applicant, and early terminated and without a negative endoscopy for ulcer within 14 days of the last dose of study drug. Therefore all of these analyses will be provided for review in this memo. Furthermore, as stated above, the Agency informed the applicant in communications on October 30, 2008, and December 17, 2009, that crude rate analyses should be performed and that these analyses must also demonstrate positive results in favor of HZT-501 for both randomized and treated populations in order to support efficacy claims for HZT-501. Therefore, this will review will focus on the crude incidence rate analyses. It is also important to note that the analysis that was agreed upon in the SPA for this protocol specified a crude rate analysis counting ONLY patients who had a document ulcer as a treatment failure using the Cochran-Mantel-Haenszel (CMH) analysis. However, as noted by the statistical team leader's memo, the applicant appeared to change the statistical analysis plan to a Kaplan

Meier method, a technique which adjusts for the “time on study” of early terminators. At that time, the statistical reviewer recommended use of a life table analysis rather than Kaplan Meier method. For labeling negotiations, the applicant used the pre-specified analysis of proportions using the CMH test. Both incidence rates and life table analyses will be reviewed in this memo.

Life table analyses for Study 301

As shown in table 9 below, the proportion of patients treated with HZT-501 who developed an upper gastrointestinal ulcer (either gastric or duodenal ulcer) for the primary population using a life-table analysis was 13.8% while the proportion of patients in the ibuprofen group was 22.6%. The difference between the treatment groups was 8.8% and was statistically significant (p 0.03).

Table 9: Proportion of patients who developed an UGI ulcer using the life-table analysis using the primary population (study 301)

	HZT-501 (N=380)			Ibuprofen (N=190)			Difference			
	Proportion ^a	SE ^b	95% CI	Proportion ^a	SE ^b	95% CI	Proportion	SE ^c	95% CI	p-value
All Subjects (N=570)	13.8%	0.022	10.1%, 18.8%	22.6%	0.034	16.7%, 30.1%	8.8%	0.040	0.8%, 16.7%	0.0304 ^c

a: Week 24 proportions are estimated from a life table analysis that included a covariate for treatment.

b: Standard errors are Greenwood estimates of the standard errors for the life table estimated Week 24 proportions.

c: p value and standard error are for the difference of the Week 24 estimated proportions of subjects developing at least one UGI ulcer.

CI Confidence Interval, SE Standard Error

However, as noted above, the applicant did not include all patients who terminated early from the study as treatment failures. Therefore, the statistical reviewer requested a re-analysis of the data with all early terminated patients treated as treatment failures (see table 10). This re-analysis produces a treatment effect for HZT-501 of 6.7%, but this finding did not reach statistical significance (p 0.12).

Table 10: Re-analysis of UGI ulcer results using life table analysis with all early terminations counted as treatment failures using the primary population (study 301)

HZT-501 (I) (N=380)		Ibuprofen (H) (N= 190)		Difference (I-H)			
Proportion ^a	SE ^b	Proportion	SE	Proportion	SE	95%CI	p-value ^c
21.3%	0.025	28.0%	0.036	6.7%	0.043	(15.2%, 1.8%)	0.1228

a: Week 24 proportions are estimated from a life table analysis that included a covariate for treatment.

b: Standard errors are Greenwood estimates of the standard errors for the life table estimated Week 24 proportions.

c: standard error are for the difference of the Week 24 estimated proportions of subjects developing at least one duodenal ulcer.

CI Confidence Interval, SE Standard Error

As shown in table 11 below, re-analysis of the data using the MITT population did not change the results and also demonstrates a treatment effect for HZT-501 of 6% but failed to reach statistical significance.

Table 11: Re-analysis of UGI ulcer results using life table analysis with all early terminations counted as treatment failures using the MITT (study 301)

HZT-501 (I) (N=390)		Ibuprofen (H) (N= 198)		Difference (I-H)			
Proportion ^a	SE ^b	Proportion	SE	Proportion	SE	95%CI	p-value ^c
21.9%	0.025	28.2%	0.036	6.3%	0.043	(-2.2%, 14.8%)	0.1433

Crude incident rate analyses for study 301

The results of the crude incident rate analysis are shown in table 12. A statistically significant treatment effect for HZT-501 of 9.5% is observed if patients who terminated early were not counted as treatment failures. However, if patients who terminated early were counted as treatment failures, the treatment effect of HZT-501 decreases slightly to 7.1% and is not statistically significant by any of the significance testing methods used by the statistical reviewer. It should be noted that in the analyses of crude incidence rates with early terminations counted as treatment failures, the number of patients in each group who terminated early with ulcers and therefore the total number of patients included in each group is slightly different in this analysis. For example, in the HZT-501 group, 75 patients terminated early, all three patients with duodenal ulcer terminated early, and 30 of 37 gastric ulcer patients terminated early. In the ibuprofen group, 33 patients terminated early, 3 of 9 duodenal ulcer patients terminated early, and 27/34 gastric ulcer patients terminated early.

Table 12: Crude incidence rates for development of ulcer by treatment group using the primary population (study 301)

Endpoint	HZT-501 (N=380)	Ibuprofen (N=190)	P-value ^a	P-value ^b	P-value ^c
	% (n/N)	% (n/N)			
UGI ulcer					
Crude rate without ET ^d	10.5% (40/380)	20.0% (38/190)	0.0028	0.0029	0.0018
Crude rate with ET ^e	30.3% (115/380)	37.4% (71/190)	0.0893	0.1072	0.0898
Gastric ulcer					
Crude rate without ET ^d	9.7% (37/380)	17.9% (34/190)	0.0070	0.0081	0.0051
Crude rate with ET ^e	30.3% (115/380)	36.8% (70/190)	0.1290	0.1371	0.1156
Duodenal ulcer					
Crude rate without ET ^d	0.8% (3/380)	4.7% (9/190)	0.0035	0.0054	0.0017
Crude rate with ET ^e	28.4% (108/380)	36.3% (69/190)	0.0679	0.0681	0.0540

a: From a Fisher's exact test;

b: From a Chi-Square test with a continuity correction adjustment;

c: From a Cochran-Mantel-Haenszel test stratified by randomization strata.

d: without including the early terminated subjects as having an ulcer;

e: including the early terminated subjects as having an ulcer.

If the MITT population is evaluated, the treatment effect for HZT-501 is 7.8%, but again this result fails to reach statistical significance (p 0.0668, Fisher's exact test).

As described above, a modified approach to the evaluation of early terminations was also performed. In this analysis, only patients who terminated the study due to adverse event, lost

to follow up, discontinued at the discretion of the investigator or sponsor, or who did not have a negative EGD for ulcer within 14 days of the last dose of study drug were included. These results are show in table 13. In this analysis of the primary population, the treatment effect of HZT-501 is 9.2% and the p-values demonstrate a significant result.

Table 13: Crude incidence rates for development of ulcer by treatment group using the primary population (study 301)

Endpoint	HZT-501 (N=380)	Ibuprofen (N=190)	P-value ^a	P-value ^b	P-value ^c
	% (n/N)	% (n/N)			
UGI ulcer					
Crude rate with modified ET	22.9% (87/380)	32.1% (61/190)	0.0199	0.0236	0.0199
Crude rate with ET ^e	30.3% (115/380)	37.4% (71/190)	0.0893	0.1072	0.0898
Gastric ulcer					
Crude rate with modified ET	22.4% (85/380)	30.0% (57/190)	0.0513	0.0597	0.0517
Crude rate with ET ^e	30.3% (115/380)	36.8% (70/190)	0.1290	0.1371	0.1156
Duodenal ulcer					
Crude rate with modified ET	13.4% (51/380)	16.8% (32/190)	0.3136	0.3342	0.2993
Crude rate with ET ^e	28.4% (108/380)	36.3% (69/190)	0.0679	0.0681	0.0540

e: including the early terminated subjects as having an ulcer.

(modified from applicant's submission dated October 20, 2010)

Taken together, the data suggest that there is a difference in the proportion of patients who develop upper gastrointestinal ulcers that favors treatment with HZT-501. However, this difference is not statistically significant when using crude incidence rate analyses and when early terminated patients are counted as treatment failures. However, based on the analysis that was agreed upon in the SPA, the results are statistically significant.

Analysis of secondary endpoints (gastric ulcer and duodenal ulcer)

Key secondary endpoints included the proportion of patients who developed a gastric ulcer or a duodenal ulcer. A statistically significant treatment effect for HZT-501 of 8.2% was observed if patients who terminated early were not counted as treatment failures. However, if the most conservative approach is used (i.e., patients who terminated early were counted as treatment failures) the treatment effect of HZT-501 decreases slightly to 6.5% and is not statistically significant by any of the significance testing methods used by the statistical reviewer (see tables 12 and 13 above). When a modified approach to the adjudication to the treatment of early termination is applied, the treatment effect is roughly the same, but the p-value increases to 0.05 (see table 13)

Sensitivity analyses

The statistical reviewer also analyzed efficacy results based on site, and noted that site 180 demonstrated a treatment effect for HZT-501 of 38%, much higher than the observed treatment effects for other sites. There were also imbalances noted by both the statistical reviewer and the clinical reviewer regarding the incidence of ulcers in women compared to men in the ibuprofen treated group. Using life table analyses, there were a higher proportion of men in the HZT-501 treatment group who developed upper gastrointestinal ulcers compared to the ibuprofen group (-15.5%; p 0.065); however, this finding was not statistically significant. It is

not clear why men in this study would have had a worse outcome. Additional analyses to evaluate this finding uncovered that there were a higher percentage of men enrolled in the study who were >65 years of age compared to women (22.2% compared to 15.8%). Additionally, there appears to be a higher proportion of patients over 65 years of age who developed gastric ulcers compared in the HZT-501 group compared to patients less than 65 years of age. Patients in the HZT-501 group who were > 65 years of age had a 13.4% incidence of development of gastric ulcers compared to 8.5% in patients less than 65 years of age. Therefore, the differences in men compared to women in the HZT-501 group may be at least partly explained by the fact that there were a higher proportion of men > 65 years of age enrolled compared to women > 65 years of age. As stated earlier, older age is a known risk factor for the development of NSAID-associated gastrointestinal ulcers.

In summary, the statistical and clinical reviewer both concluded that results from study 301 did not provide persuasive evidence that HZT-501 reduces the risk of ibuprofen-associated upper gastrointestinal ulcers in patients who require the use of ibuprofen. I agree with the primary statistical and clinical reviewers conclusion that study 301 is not persuasive if analyzed using the most conservative analysis method (including all early terminated patients as treatment failures). However, based on the SPA agreement for study 301, the applicant's pre-specified primary endpoint analysis (upper gastrointestinal ulcers) using the pre-specified analysis population (only patients with documented endoscopic ulcers counted as treatment failures) demonstrates a statistically significant result. Given the presence of the SPA agreement and the applicant's assertion that the statistical analysis agreed upon in the SPA should be used to support an efficacy claim, the applicant has demonstrated an effect of HZT-501 in the risk reduction of both upper gastrointestinal and gastric ulcers. However, I agree with the statistical team leader's conclusion that Study 301 is not persuasive on its own because the conclusions from the study depend on the assumed outcomes of early terminated patients (i.e., different analysis methods yield highly statistically variable results; p 0.03 to p 0.12).

Study 303

There were 906 patients randomized into the study; 607 patients into the HZT-501 group and 299 patients in the Ibuprofen group. All analyses by the clinical reviewer were performed on the applicant's modified intent to treat (MITT) population (only patients who had undergone at least one study-mandated follow up EGD). The MITT population included 837 patients; 561 patients in the HZT-501 group, and 276 patients in the ibuprofen group. The applicant performed analyses on their primary population, defined as patients who had at least one follow up EGD between weeks 6.7 and 26.7. The primary population included 812 patients; 550 patients in the HZT-501 group and 262 patients in the ibuprofen group. The clinical reviewer's analyses are derived from the MITT population while the statistical reviewer's analyses are derived from the primary population. It should be noted that the difference between the MITT and primary population in study 303 includes 25 patients who did not receive at least one endoscopy during the pre-defined study window (week 6.7 to week 26.7). Of these 25 patients, 5 patients in the MITT who were not counted in the primary population developed gastric ulcers (2 patients in the HZT-501 group and 3 patients in the ibuprofen group). Again, as stated above, because the MITT provides a more "inclusive" and conservative analysis of the efficacy results, the clinical reviewer used the MITT for all independent efficacy analyses. However, the statistical reviewer used the primary population

for all analyses because this was the population that the applicant had pre-specified as the analysis population. I agree with the clinical reviewer's choice to evaluate the efficacy data using the MITT population. However, the different analyses chosen by the clinical and statistical reviewer did not result in any substantive differences in the observed outcomes of the efficacy analyses for study 303.

Patients enrolled in study 301 were predominantly white (77.3%) overall, less than 65 years of age (81.7%) overall, and female (68.9%) overall. There were no significant imbalances in demographic information between treatment groups.

Overall, 394 patients (66.6%) completed the study; more patients in the ibuprofen group terminated the study early (43.1%) compared to the HZT-501 group (28.7%). The applicant reported that reasons for early termination included adverse events, patient withdrawal of consent, protocol violations, patients lost to follow-up, discretion of the investigator/sponsor, endoscopically diagnosed upper GI ulcer, or patient required excluded medication (see Table 14).

Table 14: Patient disposition for study 303 (safety population)

	HZT-501 % (n)	Ibuprofen % (n)	Total % (n)
All Patients			
Number of Patient	67.0 (607)	33.0 (299)	100.0 (906)
Completed Study	71.3 (433)	56.9 (170)	66.6 (603)
Early Termination	28.7 (174)	43.1 (129)	33.4 (303)
Reasons for Early Termination			
Death	0.0 (0)	0.3 (1)	0.1 (1)
Adverse Events	6.3 (38)	7.7 (23)	6.7 (61)
Patient Withdrawing Consent	7.9 (48)	8.7 (26)	8.2 (74)
Protocol Violations	0.2 (1)	0.3 (1)	0.2 (2)
Patient Lost to Follow-up	2.6 (16)	3.0 (9)	2.8 (25)
Discretion of Investigator/Sponsor	2.5 (15)	2.7 (8)	2.5 (23)
Endoscopically-Diagnosed UGI Ulcer	8.4 (51)	17.1 (51)	11.3 (102)
Patient Required Excluded Medication	0.2 (1)	1.0 (3)	0.4 (4)
Other	0.7 (4)	2.3 (7)	1.2 (11)

(copied from clinical review by A. Niak)

Table 15: Patient Disposition in Study HZ-CA-303 (Primary Population)

	HZT-501 % (n)	Ibuprofen % (n)	Total % (n)
All Pts.			
Number of Patient	67.7 (550)	32.3 (262)	100.0 (812)
Completed Study	78.5 (432)	65.3 (171)	74.3 (603)
Early Termination	21.5 (118)	34.7 (91)	25.7 (209)
Reasons for Early Termination			
Death	0.0 (0)	0.4 (1)	0.1 (1)
Adverse Events	3.6 (20)	4.2 (11)	3.8 (31)
Patient Withdrawing Consent	5.3 (29)	5.3 (14)	5.3 (43)
Protocol Violations	0.2 (1)	0.0 (0)	0.1 (1)
Patient Lost to Follow-up	0.9 (5)	1.5 (4)	1.1 (9)
Discretion of Investigator/Sponsor	1.8 (10)	1.9 (5)	1.8 (15)
Endoscopically-Diagnosed UGI Ulcer	8.9 (49)	19.1 (50)	12.2 (99)
Patient Required Excluded Medication	0.2 (1)	0.4 (1)	0.2 (2)
Other	0.5 (3)	1.9 (5)	1.0 (8)

(copied from clinical review by A. Niak)

Similar to the findings in study 301, patient disposition information did not change substantively for most categories if evaluating the primary population; however the number and percent of patients that discontinued due to adverse event in the HZT-501 group did decrease by nine patients (6.3% to 3.6%) when evaluating the primary population (see Table 15).

Again, as stated above, it should be noted that the most conservative approach to the analysis of results as discussed with the statistical reviewer was to include all early terminations as treatment failures, and that crude rate analyses should be performed and that these analyses must also demonstrate positive results in favor of HZT-501 for both randomized and treated populations in order to support efficacy claims for HZT-501. Additionally, it should also be noted that a special protocol agreement (SPA) was reached between the applicant and the Agency (as noted above in section 2.B). However, the applicant increased the planned size of study 303, constituting a change in the SPA and nullifying the agreement as communicated to the applicant in August, 2007. The applicant stated that the rationale for the increase in sample size was based on a more conservative reassessment incidence of ulcers in patients treated with NSAIDs and with NSAIDs plus famotidine after discussions with experts in the field and review of the literature. This protocol amendment was submitted on September 15, 2007, approximately one third into the study (study start date March 13, 2007; study end date August 13, 2008). The statistical review did not comment on the potential effect of this sample size increase, however, an increase in the sample size after the study was initiated can be concerning for possible unblinding of data, but there was no evidence of this, and the sample size change was made early in the study.

Life table analyses for Study 303

As shown in table 16 below, the proportion of patients treated with HZT-501 who developed a gastric ulcer, the primary endpoint for the study, was 12.9% while the proportion of patients in the ibuprofen group was 25.3%. The difference between the treatment groups was 12.4% and was highly statistically significant (p 0.0009).

Table 16: Proportion of patients who developed a gastric ulcer using the life-table analysis using the primary population (study 303)

	HZT-501 (N=550)			Ibuprofen (N=262)			Difference			
	Proportion ^a	SE ^b	95% CI	Proportion ^a	SE ^b	95% CI	Proportion	SE ^c	95% CI	p-value
All Subjects (N=812)	12.9%	0.017	9.8%, 16.7%	25.3%	0.033	19.5%, 32.5%	12.4%	0.037	5.1%, 19.7%	0.0009 ^c

a: Week 24 proportions are estimated from a life table analysis that included a covariate for treatment.

b: Standard errors are Greenwood estimates of the standard errors for the life table estimated Week 24 proportions.

c: p-value and standard error are for the difference of the Week 24 estimated proportions of subjects

CI = Confidence Interval, SE =Standard Error

(copied from statistical review by W.J. Chen)

Furthermore, as seen in table 17 below, a re-analysis of the data that includes all early terminations as treatment failures also demonstrates a highly statistically significant treatment effect (15%) for HZT-501.

Table 17: Re-analysis of gastric ulcer results using life table analysis with all early terminations counted as treatment failures using the primary population (study 303)

HZT-501 (N=550)			Ibuprofen (N=262)			Difference			
Proportion*	SE**	95% CI	Proportion*	SE**	95% CI	Proportion*	SE**	95% CI	p-value***
17.0%	0.019	13.6%, 21.1%	32.0%	0.034	25.8%, 39.2%	15.0%	0.039	7.4%, 22.7%	0.0001

* Week 24 proportions are estimated from a life table analysis that includes a covariate for treatment.

**Standard errors are Greenwood estimates of the standard errors for the life table estimated Week 24 proportions.

***P-value and standard error are for the difference of the Week 24 estimated proportions of subjects developing at least one ulcer.

(copied from applicant amendment to submission dated October 21, 2010, table 14.6.6.1.1)

Crude incident rate analyses for study 303

As with study 301, a crude incidence rate analysis for the primary and key secondary was also performed. The results of the crude incidence rate analysis are shown in table 18. A statistically significant treatment effect for HZT-501 (i.e., decrease incidence of gastric ulcers) of 9.8% is observed if patients who terminated early were not counted as treatment failures. Additionally, if patients who terminated early were counted as treatment failures, the treatment effect of HZT-501 actually increases slightly to 13.9% and all significance testing methods demonstrate a highly significant result. Again, as with study 301, it should be noted that in the analyses of crude incidence rates with early terminations counted as treatment failures, the number of patients in each group who terminated early with ulcers and, therefore, the total number of patients included in each group is slightly different in this analysis. For example, in

the HZT-501 group, 70 patients terminated early, 4 of 7 patients with duodenal ulcer terminated early, and 44 of 55 gastric ulcer patients terminated early. In the ibuprofen group, 40 patients terminated early, 7 of 14 duodenal ulcer patients terminated early, and 39 of 52 gastric ulcer patients terminated early.

Table 18: Crude incidence rates for development of ulcer by treatment group for study 303 (primary population)

Endpoint	HTZ-501 (N=550)	Ibuprofen (N=262)	P-value ^a	P-value ^b	P-value ^c
	% (n/N)	% (n/N)			
Gastric ulcer					
Crude rate without ET ^d	10.0% (55/550)	19.8% (52/262)	0.0002	0.0002	0.0002
Crude rate with ET ^e	23.5% (129/550)	37.4% (99/262)	<0.0001	<0.0001	<0.0001
UGI ulcer					
Crude rate without ET ^d	11.3% (62/550)	23.3% (61/262)	<0.0001	<0.0001	<0.0001
Crude rate with ET ^e	24.0% (132/550)	38.5% (101/262)	<0.0001	<0.0001	<0.0001
Duodenal ulcer					
Crude rate without ET ^d	1.3% (7/550)	5.3% (14/190)	0.0014	0.0015	0.0006
Crude rate with ET ^e	22.0% (121/550)	35.5% (93/262)	<0.0001	<0.0001	<0.0001

a: From a Fisher's exact test;

b: From a Chi-Square test with a continuity correction adjustment;

c: From a Cochran-Mantel-Haenszel test stratified by randomization strata.

d: without including the early terminated subjects as having an ulcer;

e: including the early terminated subjects as having an ulcer.

As shown in table 19, if the MITT population is evaluated, the treatment effect for HZT-501 is % for the primary endpoint (gastric ulcers), and again, this result is highly statistically significant regardless of the test used.

Table 19: Crude incidence rates for development of ulcer by treatment group for study 303 (MITT)

Endpoint	HTZ-501 % (n/N)	Ibuprofen % (n/N)	P-value ^a	P-value ^b	P-value ^c
Gastric ulcer					
Crude rate without ET ^d	10.2% (57/550)	19.9% (55/262)	0.0001	0.0001	<0.0001
Crude rate with ET ^e	25.0% (140/550)	40.9% (113/262)	<0.0001	<0.0001	<0.0001
Crude rate with modified ET	20.5% (115/561)	34.8% (96/276)	<0.0001	<0.0001	<0.0001
UGI ulcer					
Crude rate without ET ^d	11.4% (64/550)	23.3% (64/262)	<0.0001	<0.0001	<0.0001
Crude rate with ET ^e	25.5% (143/550)	41.7% (115/262)	<0.0001	<0.0001	<0.0001
Crude rate with modified ET	20.4% (112/550)	35.1% (92/262)	<0.0001	<0.0001	<0.0001
Duodenal ulcer					
Crude rate without ET ^d	1.3% (7/550)	5.3% (14/190)	0.0016	0.0020	0.0008
Crude rate with ET ^e	23.5% (132/550)	38.8% (107/262)	<0.0001	<0.0001	<0.0001
Crude rate with modified ET^f	10.7% (59/550)	17.6% (46/262)	0.0098	0.0093	0.0079

a: From a Fisher's exact test;

b: From a Chi-Square test with a continuity correction adjustment;

c: From a Cochran-Mantel-Haenszel test stratified by randomization strata.

d: without including the early terminated subjects as having an ulcer;

e: including the early terminated subjects as having an ulcer.

f: including patients counted as treatment failures who discontinued due to AE, were lost to follow-up, discontinued due to the discretion of the sponsor or investigator, or who did not have a negative endoscopy within 14 days of the last dose of study drug

As described above, a modified approach to the evaluation of early terminations was also performed that only included patients who terminated the study due to adverse event, lost to follow up, discontinued at the discretion of the investigator or sponsor, or who did not have a negative EGD for ulcer within 14 days of the last dose of study drug were included. As shown in table 19, results using the modified early termination criteria were found to be statistically significant also.

However, it should also be noted that a Division of Scientific Investigation (DSI) inspection of site 389 (Vaughn Mancha, M.D., Montgomery, AL, 257 patients enrolled) uncovered serious deficiencies in the conduct of the study at this site (for additional information see section 11.B). As a result of these deficiencies, the investigator was issued a Warning Letter on February 17, 2011. Furthermore, the DSI reviewer concluded that the study was not conducted adequately at site 389, and that data generated from this site should not be used in support of the of the NDA. Therefore, a re-analysis of the data with site 389 was excluded was performed. There were 153 patients removed from the MITT population from site 389 (104 patients assigned to the HZT-501 group and 49 patients assigned to the ibuprofen group). Additionally, the review division questioned the conduct of study 303 based on the findings of the inspection at site 389 and felt that additional information to establish the validity of the results from study 303 was necessary. Therefore, the review division requested additional DSI inspections at two additional sites (site 340 and site 363). These two additional sites for study 303 were requested because these sites had large number of patients who were terminated from the study early. Late in the review cycle, results of the DSI inspection at site 363 uncovered additional deficiencies that called the validity of the data in four patients into question (patient 005,021,050, and 100). The DSI reviewer recommended that these four patients also be excluded from all efficacy analyses. The reasons for the exclusion of these four patients were variable and included dispensing of the wrong drug in one patient, missing study kit number in one patient, missing records for one patient, and dispensing of the wrong kit and error in specified dose of study medication. I agree with the DSI reviewer’s recommendation to exclude data from these four patients. Table 20 shows the revised results of the crude incidence rate of gastric ulcers when these data from site 389 and four patients from site 363 are removed. There is no substantive effect on the overall results with these data removed.

Table 20: Gastric ulcer crude incidence rate gastric ulcer including early terminated patients as treatment failures using the primary population (excluding patients from site 389 and 4 patients for site 363)

	HZT-501 (H) (N 445)	Ibuprofen (I) (N 214)	Difference (I-H)		
	Proportion	Proportion	Proportion	95% CI	<i>p-value</i>
All Patients (N 659)	21.60% (96/445)	37.0% (79/214)	15.40%	(-23.0%, -8.0%)	< 0.0001

In summary, all of the analyses (i.e., all life table analyses, all crude incidence rates, with and without early terminated patients counted as treatment failures, and excluding patients from

site 389 and site 363) from this study for the primary endpoint of gastric ulcers demonstrates a decrease in the proportion of patients treated with HZT-501 who developed gastric ulcers that was statistically significant.

Sensitivity analyses

The statistical reviewer also analyzed efficacy results based on site, and noted that there were no substantive differences in efficacy data obtained from larger sites (i.e., sites that enrolled at least 30 patients). Based upon the statistical reviewer’s evaluation using sites that enrolled at least 30 patients, there were no substantive differences when comparing these sites to the overall results of study 303. Accordingly, it appears that no particular site is deemed to dominate the superiority of HTZ-501 to ibuprofen.

For the following sub-group analyses, the MITT was used with site 389 excluded (459 patients randomized to the HZT-501 group, and 225 patients randomized to the ibuprofen group). These numbers are slightly different than used by the statistical reviewer because the statistical reviewer evaluated the primary population when excluding site 389. However, these differences are small and do not appear to have affected these analyses substantively.

As stated above, advanced age, concomitant use of low-dose aspirin, other NSAIDS, anti-coagulants, and previous history of peptic ulcer or serious UGI complication from NSAID use increases the risk of NSAID-associated UGI ulcers. Therefore, an analysis of the effect of advanced age, concomitant use low-dose aspirin, and a previous history of UGI ulcer was also conducted. Tables 21-23 show the results of these subgroup analyses for study 303.

Table 21: Gastric ulcer incidence in patients taking low-dose aspirin study 303 (MITT with site 389 excluded)

Treatment N (%)	Gastric Ulcer Incidence N (%)
HZT-501: 67/459 (14.6)	10 (14.9)
Ibuprofen: 25/225 (11.1)	6 (24)

In study 303, approximately 15% of patients in the HZT-501 group were taking low-dose aspirin and approximately 11% of patients in the ibuprofen group. The incidence of gastric ulcer in the HZT-501 group was 15% and 24% in the ibuprofen group. These data suggest that HZT-501 may also be effective in patients taking low-dose aspirin.

Table 22: Gastric ulcer incidence in patients based on age study 303 (MITT with site 389 excluded)

Treatment N (%)	Gastric Ulcer Incidence N (%)
HZT-501 <65 years of age 367/459 (80)	25 (6.8%)
HZT-501 ≥ 65 years of age 92/459 (20)	17 (18.4%)
Ibuprofen < 65 years of age 176/225 (78)	29 (16.4%)
Ibuprofen ≥65 years of age 49/225 (22)	9 (18.4%)

Additionally, data on the effect of HZT-501 in development of gastric ulcers in based on age is presented in table 22. The incidence of gastric ulcers was lower only in patients taking HZT-501 who were less than 65 years of age. The incidence of gastric ulcers was similar between patients taking HZT-501 \geq 65 years of age and both ibuprofen groups. This finding suggests that HZT-501 may not be effective in decreasing the risk of gastric ulcers in patients \geq 65 years of age. It is also important to note that despite the smaller number of patients \geq 65 years of age in the study, this group represents a high-risk group in which the treatment effect of HZT-501 would be expected to be more robust. Therefore, fewer patients would be required to demonstrate a statistically significant effect. In this case, the treatment effect not larger, indeed, there was no treatment effect evident at all.

Table 23: Gastric ulcer incidence in patients with a history of gastrointestinal ulcer for study 303 (MITT with site 389 excluded)

Treatment N (%)	Gastric Ulcer Incidence N (%)
HZT-501: 34/459 (7.4)	7 (20.5)
Ibuprofen: 13/225 (5.7)	3 (23.1)

Furthermore, as shown in table 23, in patients with a previous history of gastric ulcers, the incidence of gastric ulcers in the HZT-501 group was only marginally lower than for the ibuprofen group (20.5% compared to 23.1%). Again, it is also important to note that despite the smaller number of patients without a prior history of gastric ulcers in the study, this group represents a high-risk group in which the treatment effect of HZT-501 would be expected to be more robust. Therefore, fewer patients would be required to demonstrate a statistically significant effect. In this case, the treatment effect not larger, indeed, there was a *worse outcome* for patients treated with HZT-501 compared to ibuprofen. Nevertheless, these subgroup analyses were not powered appropriately to allow for any clear statistical inferences. However, it appears that famotidine may not be effective in reducing the risk of gastric ulcers in certain high-risk patients (e.g., patients \geq 65 years of age or with a prior history of gastrointestinal ulcers).

Discussion of overall efficacy results

The applicant provided two phase 3 studies evaluating the proportion of patients who require long-term ibuprofen therapy who develop upper gastrointestinal ulcer (either gastric or duodenal ulcers) taking HZT-501 compared to ibuprofen alone. Prior to the submission of the NDA by the applicant, the Agency clearly informed them of specific required analyses of efficacy that the applicant should include. In a communication with the applicant in October, 2008 and again during the pre-NDA meeting (as described above in section 2.B) the division informed the applicant that crude incident rate analyses for development of ulcers would be required and that demonstration of an effect based on these analyses would be necessary to support approval and labeling for the product. While the statistical reviewer stated in his review that the pre-specified primary analysis is the life-table analysis, crude incident rate analyses were also reviewed and considered to be necessary to support approval and labeling of the product. Therefore, both the life table analyses and the crude incident rate analyses were reviewed and these results were generally consistent within and across studies.

For study 301, the statistical and clinical reviewer both concluded that results from study 301 did not provide persuasive evidence that HZT-501 reduces the risk of ibuprofen-associated upper gastrointestinal ulcers in patients who require the use of ibuprofen. The data did not provide robust evidence of effect because the conservative approach to the statistical analyses (i.e., inclusion of all patients who terminated early as treatment failures) was not statistically significant for either life table or crude incident rate analyses. Even with the applicant's "most liberal" approach (including only patients with ulcers who terminated early as treatment failures, the life table and crude incident rate analyses are only marginally statistically significant. I agree with the statistical and clinical reviewer that study 301 does not provide persuasive evidence of the efficacy of HZT-501 if analyzed using the most conservative analysis method (including all early terminated patients as treatment failures). However, based on the SPA agreement for study 301, the applicant's pre-specified primary endpoint analysis using the pre-specified analysis population demonstrates a statistically significant result. Given the presence of the SPA agreement and the applicant's assertion that the statistical analysis agreed upon in the SPA should be used to support an efficacy claim, the applicant has reasonably demonstrated an effect of HZT-501 in the risk reduction of both upper gastrointestinal and gastric ulcers.

In study 303, both the statistical and clinical reviewer both concluded that results from study 303 provided persuasive evidence that HZT-501 reduces the risk of ibuprofen-associated gastric ulcers based on the highly statistically significant efficacy results for both life table and crude incident rate analyses whether or not early terminated patients are considered treatment failures. Again, it is also important to note that despite the smaller number of patients without a prior history of gastric ulcers or patients ≥ 65 years of age in the study, these group represents high-risk groups in which the treatment effect of HZT-501 would be expected to be more robust. Therefore, fewer patients would be required to demonstrate a statistically significant effect. In both case, the treatment effect not larger, indeed, there was a *worse outcome* for patients treated with HZT-501 compared to ibuprofen with a prior history of upper gastrointestinal ulcers. Again, the data with regard to high-risk populations were limited and therefore, it is not clear that HZT-501 is effective in reducing the risk of ibuprofen-associated gastric ulcers in this population.

In the pooled analyses for efficacy in patients ≥ 65 years of age or with a prior history of upper gastrointestinal ulcers, 24% of patients in the HZT-501 group developed ulcers while 27% of ibuprofen treated patients developed ulcers. This difference would be expected to be larger than the overall results for the studies because these patients were high risk. Indeed, the difference was only 1/3 of that observed for upper gastrointestinal ulcers. The results for the pooled analysis for patients with a prior history of gastrointestinal ulcer were even more concerning. In the HZT-501 group, 25% of patients developed an upper gastrointestinal ulcer while only 24% of patients in the ibuprofen group developed ulcers. Thus, it is not clear that treatment with HZT-501 in patients 65 years of age and older, or in patients with a prior history of upper gastrointestinal ulcers is effective.

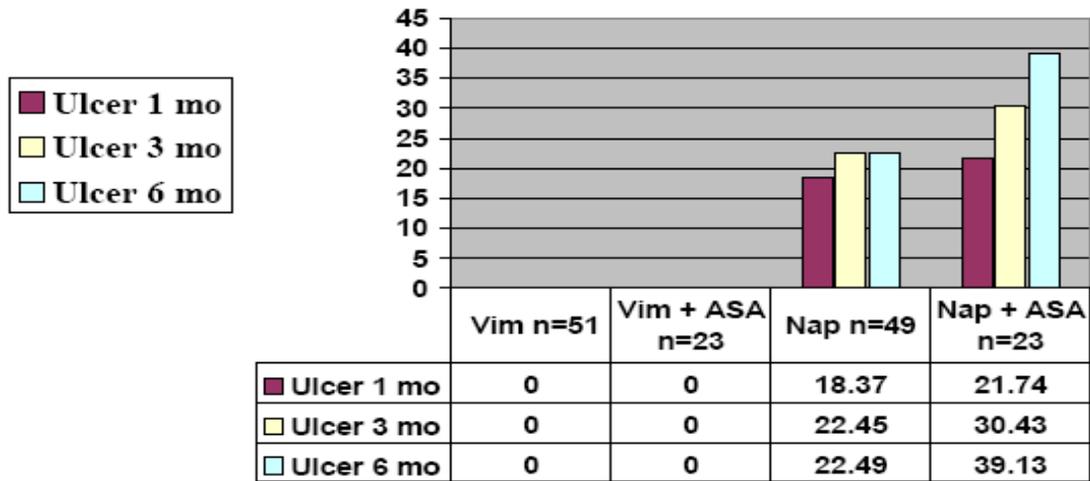
Registration endoscopy trials of PPIs to evaluate the risk reduction of NSAID-associated gastric ulcers have been 3 to 6 month, randomized, placebo-controlled and/or active-controlled trials in patients who required chronic use of NSAIDs. Patients had to have no evidence of

ulcers on baseline upper endoscopy. Patients were treated with NSAIDs and were randomized to a PPI or placebo and underwent upper endoscopies to assess for GUs and DUs. Table 24 displays the GU treatment effects of approved gastroprotective products compared to placebo in endoscopy trials of NSAID-treated patients. Table 16 also displays the results of a published study that evaluated esomeprazole for the risk reduction of GUs in low-dose aspirin-treated patients¹³ and a comparison of the risk factors for NSAID-associated UGI toxicity across the endoscopy trials.

The difference in the incidence of ulcers between the gastroprotective products and control groups (observed risk difference) ranged from 7% to 29%. The variability in the range of risk difference may be related to the differences in the underlying risk of NSAID-associated UGI toxicity in the patient populations enrolled in the trials. Endoscopy trials which enrolled patients with lower risk of UGI toxicity, found both a lower incidence of GUs in the control group and a lower risk difference between the gastroprotective product and the control group. In a published trial investigating the impact of esomeprazole on the use of low-dose aspirin, the relative decrease in risk of GUs was 0.3; however, the observed difference in proportion of patients who had GUs was only 3%. High risk patients (i.e., patients ≥ 65 years of age, and patients with a previous history of gastrointestinal ulcers) from study 303 showed even lower risk reduction in gastric ulcers compared to control. The gastrointestinal drugs advisory committee (GIDAC) meeting was held on November 4, 2010 to discuss the use clinical outcomes and endoscopy trials to assess GI complications of NSAID use. The committee voted 8 to 4 in favor of the use of endoscopically-diagnosed gastric/duodenal ulcers as an adequate primary endpoint for evaluating products intended to prevent NSAID-associated upper GI toxicity. It should be noted that those who voted “No” also emphasized concerns regarding the reproducibility and standardization of endoscopic trials, and suggested that GI bleeding as a clinically meaningful endpoint for such trials.

The difference in the incidence of ulcers between the HZT-501 treatment group and the ibuprofen treatment group in study 303 (15.4%) is clearly in the range seen with PPIs approved for the reduction in risk of NSAID-associated gastric ulcers overall. Interestingly, the phase 3 studies for HZT-501 generally enrolled a population that was at lower risk for the development of ulcers because patients with a history of serious GI complications were excluded from study, patients were not required to have a history of gastrointestinal ulcer in the past, and overall the patients studied in study 303 were younger (mean age 55.4 years). Despite enrolling a lower risk population, the treatment effect was similar to studies that enrolled high risk patients. However, high-risk populations (i.e., patients ≥ 65 years of age, and patients with a previous history of gastrointestinal ulcers) did not appear to benefit from treatment with HZT-501. Data from the clinical review for Vimovo demonstrate a substantive difference in the effect of Vimovo in patients 65 years of age and older for with low-dose aspirin and no low-dose aspirin treatment (see figure 3). As shown in figure 3, treatment with Vimovo in patients ≥ 65 years of age resulted in no ulcer development compared with approximately 20-40% of patients developing ulcers without Vimovo. These data suggest that HZT-501 may not be as effective as Vimovo in high risk patients (e.g., patients 65 years of age and older including those patients taking low-dose aspirin).

Figure 3 Cumulative Incidence of Patients Developing Gastric Ulcers in Participants \geq 65 years old with and without Low-Dose Aspirin Use PN400-301



(copied from clinical review for Vimovo by E. Wynn, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022511Orig1s000MedR.pdf)

Furthermore, it appears that the incident rates of gastric ulcers in the HZT-501 treated groups in both studies (10-11%) is substantially higher than the rates for gastric ulcer in other studies as described below (1-7%). One exception is the lansoprazole study in which the ulcer rate was 20%, although this study enrolled a very high risk population and the ulcer rate would be expected to be higher for both treated and untreated groups. Thus, it can be inferred from this comparison that HZT-501 does not appear to provide as much risk reduction in patients at risk of developing NSAID-associated gastric ulcers compared to other PPIs. However, clear conclusions regarding the relative efficacy of HZT-501 compared to other PPIs cannot be made because of this cross study comparison. Nevertheless, it should be clearly stated in labeling that HZT-501 was not studied in the highest risk patients.

Table 24: Risk difference and relative risk of gastric ulcers for gastroprotective products compared to placebo control in 3-6 month endoscopy trials

	Incidence of GUs	Risk Difference ²	Relative Risk (95% CI) ³	Risk Factors	NSAIDs Used
Misoprostol ± NSAIDs					
Misoprostol Endoscopy Study 1 (12 weeks) – EGD at Weeks 0, 4, 8, and 12					
Misoprostol 200 µg QID (n=74)	1 %	24%	0.1 (<0.1, 0.4)	Mean age = 74 years old Hx of ulcer = 18%	ibuprofen, piroxicam, naproxen
Placebo (n=76)	25%				
Misoprostol Endoscopy Study 2 (12 weeks) – EGD at Weeks 0, 4, 8, and 12					
Misoprostol 200 µg QID (n=65)	3%	15%	0.2 (<0.1, 0.8)	Mean age = 60 years old Hx of ulcer = 7%	ibuprofen, piroxicam, naproxen
Placebo (n=62)	18%				
PPIs ± NSAIDs					
Lansoprazole Study (12 weeks) – EGD at Weeks 0, 4, 8, and 12					
Lansoprazole 15 mg/day (n=136)	20%	29%	0.4 (0.3, 0.6)	Mean age 60 years Hx of GU = 99% Hx of DU = 50% Low dose aspirin use = 19%	ibuprofen, piroxicam, naproxen, diclofenac
Placebo (n=133)	49%				
Esomeprazole Study 1 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole 20 mg/day (n=191)	5%	7%	0.4 (0.2, 0.9)	Mean age = 64 Hx of PUB 26% Hx of POB = 1% Low dose aspirin use = 10%	COX-2 = 14% Non-selective = 85%
Placebo (n=184)	12%				
Esomeprazole Study 2 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole 20 mg/day (n=267)	5%	12%	0.3 (0.1, 0.5)	Mean age = 66 Hx of PUB = 10% Hx of POB = 1% Low dose aspirin use = 12%	COX-2 = 39% Non-selective = 61%
Placebo (n=257)	17%				
Esomeprazole/Naproxen Study 1 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole/naproxen (20/500 mg) BID (n=218)	4%	19%	0.2	Mean age = 60 Hx of PUB =5% Low dose aspirin use = 24%	Naproxen
Naproxen 500 mg BID (n=216)	23%				
Esomeprazole/Naproxen Study 2 (26 weeks) – EGD at Weeks 0, 4, 12, and 26					
Esomeprazole/naproxen (20/500 mg) BID (n=210)	7%	17%	0.3	Mean age = 60 Hx of PUB = 11% Low dose aspirin use = 23%	Naproxen
Naproxen 500 mg BID (n=210)	24%				
Esomeprazole ± Low-Dose Aspirin (75 to 325 mg) – 26 week study¹³ EGD at Weeks 0, 8, and 26					
Esomeprazole 20 mg (n=493)	1%	3%	0.3	Mean age = 69	Low dose aspirin
Placebo (n=498)	4%				

¹ The primary endpoint for some of these endoscopy trials was the proportion of patients without GUs during the treatment period. Although in other trials, the primary endpoint was the proportion of patients free from GUs, the data are presented as the proportion of patients without GUs for consistency.

² The risk difference was the difference between the incidence of GUs in the control group and the gastroprotective product group.

(copied from GIDAC advisory briefing document, “Outcome Measures for Claims to Reduce NSAID-Associated Upper Gastrointestinal (UGI) Toxicity,” November 4, 2010, available at <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/ucm195280.htm>)

The data presented by the applicant in this submission provides substantial evidence to support the approval of the product. Study 303 provided a reduction in the incidence of endoscopically diagnosed gastric ulcers that is comparable to other approved products for this indication and what the GI drugs advisory committee agreed to be clinically meaningful. Furthermore, the results of this study were highly statistically significant. The results of study

301 did not reach statistical significance when evaluated using the most conservative approach. However, based on the use of the pre-specified primary analysis for the primary endpoint in study 301 (upper gastrointestinal ulcers) the applicant was able to demonstrate a statistically significant difference. Therefore, given this agreement under SPA, it is the opinion of the Division that labeling could reasonably include the risk reduction of upper gastrointestinal ulcers. Nevertheless, it is my opinion that the applicant has not provided sufficient evidence that HZT-501 reduces the risk of duodenal ulcers in patients requiring ibuprofen treatment. Duodenal ulcers are strongly associated with H. pylori infection and H. pylori eradication before starting NSAID therapy virtually abolishes the risk of duodenal ulcers (Venerito M., Helicobacter 15:239-250). Patients who were H. pylori positive were excluded from the study; however, if a patient subsequently developed a duodenal ulcer, H. pylori testing was not performed. Therefore, it is unclear whether the development of a duodenal ulcer was related to use of ibuprofen or development of H. pylori infection. Additionally, the incidence of duodenal ulcers in both studies is quite low and therefore the ability to detect a true difference may be more difficult. Furthermore, in products approved to reduce the risk of NSAID associated ulcers, only gastric ulcers have been approved. Finally, in a recent approval for Vimovo, a PPI (esomeprazole) and NSAID (naproxen) combination product, the incidence of duodenal ulcers was considered an exploratory endpoint because the incidence of ulcers was low, and the applicant had not clearly defined their planned analysis for this endpoint prospectively.

Another limitation in the data submitted are the small numbers of patients studied in clinical trials that were at high risk for development of gastrointestinal ulcers (e.g., patients over 65 years of age, patients taking concomitant low-dose aspirin, and patients with a prior history of gastrointestinal ulcers). Approximately 15% of the patients in the study were taking low-dose aspirin, and in this subgroup, the effect of HZT-501 appeared to provide benefit (9% decrease in incidence of gastric ulcers compared to ibuprofen), but this sub-group analysis was performed post-hoc, and the population was small. Furthermore, sub-group analyses for patients ≥ 65 years of age and with a history of previous gastrointestinal ulcer failed to show any benefit in the effect of HZT-501 compared to ibuprofen alone. Again, these analyses were performed post-hoc and evaluated very small numbers of patients. Nevertheless, given the failure to provide adequate data to evaluate the effect of HZT-501 in high-risk populations, the product should clearly indicate the limitations of the clinical studies including the limited efficacy information for certain high risk groups.

Finally, the applicant is seeking an indication to allow for use of HZT-501 (b) (4). However, the only indication approved for the 800 mg, tid, dose is the treatment of osteoarthritis and rheumatoid arthritis. (b) (4)

Therefore, I conclude that the applicant has demonstrated substantial evidence of effectiveness of the famotidine component of HZT-501 for the reduction of risk in the development of ibuprofen-associated gastric ulcers in patients who require the use of ibuprofen for treatment of osteoarthritis and rheumatoid arthritis. The data for upper gastrointestinal ulcers may be reasonably used to support labeling because the pre-specified primary analysis using the pre-

specified analysis population was statistically significant. However, I agree with the clinical and statistical reviewer that using the most conservative analysis, the study fails to demonstrate a statistically significant result. I also conclude that the indication should not include reduction of risk for duodenal ulcers. I also recommend that labeling should state that HZT-501 there were limitations in the study, and that high risk groups (i.e., patients ≥ 65 years of age, patients with a history of gastrointestinal ulcers, and patients taking low-dose aspirin or other anticoagulants) were not adequately studied. Furthermore, data in patients patients ≥ 65 years of age, patients with a history of gastrointestinal ulcers appear to show that HZT-501 does not work as well as other products used to reduce the risk of NSAID-associated gastric ulcers already marketed and may not be better than no treatment.

8. Safety

The reader is referred to the clinical review by A. Niak, dated April 22, 2011 for complete information.

The active ingredients in HZT-501, ibuprofen and famotidine, have been commercially available in the US since 1974 and 1981, respectively. Thus, the individual safety profile of each of these drugs has been well characterized. Additionally, as noted above in the clinical pharmacology review, there are no significant interactions between ibuprofen and famotidine resulting in increased exposure for either drug when given together. Unlike, proton pump inhibitors, however, H₂ receptor antagonists, including famotidine, have not previously been approved in the US for risk reduction or prevention of NSAID associated gastric ulcers.

The primary safety data for HZT-501 come from the two phase 3 trials, study 301 and study 303. Additionally the extension study for these two studies, study 304 was also reviewed, but these data were not combined with the primary safety population. The primary safety database consisted of 1533 patients, all of whom received at least one dose of study drug in studies 301 or 303; 1022 patients received HZT-501 and 511 received ibuprofen, 800 mg (see table 25). Of these 1533 patients, a total of 179 patients continued to receive treatment in study 304, with 132 continuing treatment with HZT-501, and 36 patients continuing treatment with ibuprofen, 800 mg, for a total of 1 year of treatment.

Table 25: Primary safety population

	HZ-CA-301	HZ-CA-303
Number of patients receiving HZT-501	415	607
Number of patients receiving ibuprofen	212	299
Total number of patients (1533)	627	906

(copied from Clinical Review by A. Niak)

As described above in the efficacy section, the demographics of the safety population were similar across the two treatment groups with no statistically significant differences except for ethnicity (more Hispanic patients were assigned to treatment with HZT-501 than ibuprofen). Patients in both treatment groups were predominantly white, female, and less than 65 years of age. As expected, the demographic data from the extension study were also similar.

Drop outs due to Adverse Events

The disposition of patients in the safety population is shown in Table 26. There was a statistically significant difference in the number of patients who dropped out of the study in the ibuprofen group compared to the HZT-501 treated group. The reasons for early termination are also provided in the table, and there were no significant differences in the proportion of patients that dropped out of the study due to an adverse event across the treatment groups. The types of adverse events leading to discontinuation were not statistically significant for any adverse event except dyspepsia. Five patients (0.5%) discontinued due to this AE in the HZT-501 group while nine patients (1.8%) in the ibuprofen group discontinued due to dyspepsia (p 0.01). However, this difference is difficult to interpret because of the subjective nature of this AE, and because measurement of this AE was not standardized.

Table 26: Disposition of patients in the primary safety database

	HZT-501 % (n)	Ibuprofen %(n)	Total %(n)
Number of Subjects	100.0 (1022)	100.0 (511)	100 (1533)
Completed Study	69.0 (705)	57.1 (292)	65.0 (997)
Early Termination	31.0 (317)*	42.9 (219)*	35.0 (536)
Reasons for Early Termination:			
Death	0 (0)	0.2 (1)	0.1 (1)
Adverse Event	6.1 (62)	7.4 (38)	6.5 (100)
Withdrew Consent	8.9 (91)	10.2 (52)	9.3 (143)
Protocol Violation	0.6 (6)	0.2 (1)	0.5 (7)
Lost to Follow Up	3.7 (38)	2.7 (14)	3.4 (52)
Discretion of Investigator/Sponsor	2.4 (25)	3.3 (17)	2.7 (42)
Endoscopically Diagnosed UGI Ulcer	8.2 (84)	16.6 (85)	11.0 (169)
Required Excluded Medication	0.2 (2)	0.8 (4)	0.4 (6)
Other	0.9 (9)	1.4 (7)	1.0 (16)

*p<0.0001 comparing study completers and those that terminated early between the treatment groups, controlling for study

(copied from applicant's Summary of clinical Safety, 2.7.4, page 19/255)

In the extension study, there were not substantive differences in the dropout rates between the two treatment arms (see table 27). Interestingly, early terminations in the HZT-501 treated group during the extension period were similar to the ibuprofen treatment period, although one would have expected a higher drop out rate due to adverse events or development of ulcers. However, endoscopy was not performed during the extension period, leading this reviewer to question whether endoscopically diagnosed ulcers can be considered a clinically meaningful endpoint if one assumes that endoscopically diagnosed ulcers ultimately lead to clinical symptoms and identifiable adverse events. As noted above, the GIDAC voted 8 to 4 in favor of the use of endoscopically-diagnosed gastric/duodenal ulcers as an adequate primary

endpoint for evaluating products intended to prevent NSAID-associated upper GI toxicity. However, those who voted “No” also emphasized concerns regarding the reproducibility and standardization of endoscopic trials, and suggested that GI bleeding as a clinically meaningful endpoint for such trials.

Table 27: Disposition of patients during the extension study (Study 304)

	HZI-501 % (n)	Ibuprofen %(n)	Total %(n)
Number of Subjects	100.0 (132)	100.0 (47)	100 (179)
Completed Study	84.8 (112)	80.9 (38)	83.8 (150)
Early Termination	15.2 (20)	19.1 (9)	16.2 (29)
Reason for Early Termination:			
Death	0 (0)	0 (0)	0 (0)
Adverse Event	2.3 (3)	2.1 (1)	2.2 (4)
Withdrew Consent	4.5 (6)	6.4 (3)	5.0 (9)
Protocol Violation	0 (0)	0 (0)	0 (0)
Lost to Follow Up	5.3 (7)	4.3 (2)	5.0 (9)
Discretion of Investigator/Sponsor	1.5 (2)	2.1 (1)	1.7 (3)
Endoscopically Diagnosed UGI Ulcer*	0 (0)	0 (0)	0 (0)
Required Excluded Medication	0 (0)	2.1 (1)	0.6 (1)
Other	1.5 (2)	2.1 (1)	1.7 (3)

(copied from applicant’s Summary of clinical Safety, 2.7.4, page 20/255)

Deaths and Serious Adverse Events

There was one death in the phase 3 trials in patient assigned to the ibuprofen treatment group (study 303). The patient was a 48 year-old white female with a significant past medical history to include bilateral knee replacement surgery (in 2003), osteoarthritis, low back pain, chronic obstructive pulmonary disease, hypercholesterolemia, cold sores, hypertension, depression, anxiety, chronic sinusitis, hypothyroidism, allergy to morphine and penicillin, carpal tunnel syndrome, and hiatal hernia. Relevant medications taken at the time of the event included lisinopril, lovastatin, levothyroxine, tiotropium bromide (Spiriva), clonazepam, risedronate sodium (Actonel), calcium, hydrocodone/acetaminophen (Lortab), diazepam (Valium), citalopram, mitrazepine, vitamin B, and tramadol. The cause of death was attributed to cardiopulmonary arrest and multisystem organ failure due to acute acetaminophen poisoning, although it does not appear that this poisoning was intentional. The investigator reported that the death was not likely related to the study medication. The primary clinical reviewer agreed with this assessment.

A total of 50 patients in the primary safety database developed a treatment emergent serious adverse event (SAE). There were 33 patients (3.2%) with SAEs in the HZI-501 group and 17 patients (3.3%) in the ibuprofen group. There were no substantive imbalances in the types or numbers of SAEs between treatment groups, including cardiovascular SAEs, gastrointestinal

SAEs, or infection-related SAEs. There was also a small imbalance in the development of acute renal failure. Three patients in the HZT-501 treatment group developed a serious adverse event of acute renal failure while no cases of acute renal failure were reported for the ibuprofen group. All of the patients who developed acute renal failure had a history of diabetes mellitus and were taking medications that could also predispose for the development of acute renal failure (i.e., diuretic treatment and/or angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers). Upon further review of the medical history provided in the safety population, there appears to be an equal distribution of patients with a medical history of hypertension (12.2% in the HZT-501 group and 11.7% in the ibuprofen group, respectively) and diabetes mellitus (10% in the HZT-501 group and 10.4% in ibuprofen groups, respectively) between the treatment groups.

Eleven serious adverse events occurring during the extension study. No patients who had experienced a serious adverse event (SAE) while participating in study 301 or 303 were enrolled into the extension study. The incidence of serious adverse events was similar between treatment groups; 8 patients (6.1%) in the HZT-501 group and 3 patients (6.4%) in the ibuprofen group. Again, there were no substantive imbalances in the types or numbers of SAEs between treatment groups, including cardiovascular SAEs, gastrointestinal SAEs, or infection-related SAEs.

Significant Adverse Events

There was also an apparent imbalance in the number of patients who developed increases in hypertension during the study (see table 29). Additionally, there was a slight imbalance in the overall number of patients who developed increase in serum creatinine (0.9% or 9 patients for HZT-501 and 0.7% or 2 patients for ibuprofen). However, upon further review of these creatinine shifts, that data are not conclusive (see table 30). There was a higher incidence increase in serum creatinine in the HZT-501 group in Study 301, but the reverse was seen in Study 303. Thus, it remains unclear whether treatment with HZT-501 may exacerbate the development of renal complications including acute renal failure but it is already known that ibuprofen can produce these complications and the labeling has been updated to communicate to prescribers that monitoring for the development of nephrotoxicity should be considered. Additionally, the labeling was updated to recommend that patients with moderate to severe renal insufficiency (GFR <50 cc/min) should not take HZT-501.

The labeling for ibuprofen includes a boxed warning for the risk of cardiovascular events including myocardial infarction, and stroke, and is contraindicated for treatment of pain in the setting of coronary artery bypass graft surgery. The boxed warning also includes an increased risk of serious gastrointestinal adverse events including bleeding, ulceration, and perforation of the stomach or intestines. There was not increase in these types of adverse events for either the HZT-501 group or the ibuprofen treated groups in the primary safety population or extension studies.

The labeling for famotidine does not carry a boxed warning. Significant adverse events that are included in famotidine labeling include arrhythmias, liver enzyme abnormalities, agranulocytosis, pancytopenia, leucopenia, thrombocytopenia, anaphylaxis, seizures, toxic epidermal necrolysis, and psychiatric disturbances.

Common Adverse Events

The clinical reviewer evaluated common adverse events occurring in $\geq 3\%$ of the safety population (see table 28). In the patients receiving the HZT-501, 55.0% of the patients exhibited at least one adverse event and 59% of patients had at least one adverse event in the ibuprofen group. The most common adverse events overall were dyspepsia and nausea. The types of adverse events observed in the primary safety database as well as the extension study are consistent with adverse events that are already described in patient labeling for famotidine and ibuprofen.

Table 28: Adverse events in the primary safety database with incidence $\geq 3\%$

	HZT-501 (N 1022)	Ibuprofen (N 511)	Total (N 1533)
Preferred Term	% (n)	% (n)	% (n)
Total patients with adverse event	55.0 (562)	58.7 (300)	56.2 (862)
Gastrointestinal Disorders			
Dyspepsia	4.7 (48)	8.0 (41)	5.8 (89)
Nausea	5.8 (59)	4.7 (24)	5.4 (83)
Diarrhea	4.6 (47)	4.3 (22)	4.5 (69)
Constipation	4.1 (42)	4.1 (21)	4.1 (63)
Abdominal Pain -Upper	3.3 (34)	2.5 (13)	3.1 (47)
Infections and Infestations			
Upper Resp. Tract Infect.	3.8 (39)	4.1 (21)	3.9 (60)
Nasopharyngitis	2.4 (25)	2.7 (14)	2.5 (39)
Nervous System Disorders			
Headache	3.3 (34)	3.3 (17)	3.3 (51)

Additionally, in order to ascertain the types of common adverse events that could be related to HZT-501 treatment, adverse events that were observed more commonly in the HZT-501 group compared to the ibuprofen group were also evaluated. Table 29 shows adverse reactions seen in at least 2% of the HZT-501 group, and in greater frequency than the ibuprofen treatment group. While these analyses are not powered statistically to clearly establish a difference, these adverse reactions should be included in patient labeling to evaluate common adverse reactions that could be related to treatment with HZT-501.

Table 29: Incidence of Adverse Reactions occurring in at least 2% of HZT-501 patients and in greater frequency than in the ibuprofen treatment group

	HZT-501 N 1022	Ibuprofen N 511
	%	%
Blood and lymphatic system disorders		
Anemia	2%	1%
Gastrointestinal disorders		
Nausea	6%	5%
Diarrhea	5%	4%

	HZT-501 N 1022	Ibuprofen N 511
	%	%
Abdominal pain upper	3%	3%
Vomiting	2%	2%
Stomach discomfort	2%	2%
General disorders and administration site conditions		
Edema peripheral	2%	2%
Infections and infestations		
Bronchitis	2%	1%
Musculoskeletal and connective tissue disorders		
Back pain	2%	1%
Respiratory, thoracic and mediastinal disorders		
Pharyngolaryngeal pain	2%	1%
Vascular disorders		
Hypertension	3%	2%

Expanded safety population

The expanded safety population includes patients who participated in other clinical trials for HZT-501.

Laboratory Investigations and Vital Signs

In general, there were not substantive changes from baseline in clinical laboratory parameters and changes were comparable between the two treatment groups. However, as noted above, there was a slight imbalance in the number of serious adverse events of acute renal failure in the HZT-501 group. Therefore, changes in serum creatinine were of special interest. As shown in table 30, there was no clear difference in increases in serum creatinine identified. There was a higher percentage of patients who had an increase in serum creatinine in the HZT-501 treatment group in study 301, but the reverse was true for study 303. As described above, and in section 12: Labeling, additional language has been added to labeling to instruct prescribers to monitor for signs and symptoms of nephrotoxicity. Additionally, the labeling was updated to recommend that patients with moderate to severe renal insufficiency (GFR <50 cc/min) should not take HZT-501.

Table 30: Shift table of serum creatinine, normal** to abnormal*** in controlled studies

Baseline	Post-Baseline*	Study 301		Study 303	
		DUEXIS N 414 % (n)	Ibuprofen N 207 % (n)	DUEXIS N 598 % (n)	Ibuprofen N 296 % (n)
Normal**	Abnormal***	4 (17)	2 (4)	2 (15)	4 (12)

*At any point after baseline level

**serum creatinine normal range is 0.5 – 1.4 mg/dL or 44-124 micromol/L

***serum creatinine >1.4 mg/dL

Vital sign values were collected in study 301 and 303 at Screening, at Baseline (Study Day 0), and at Weeks 4, 8, 16, and 24. In the extension study, vital sign values were collected at Baseline (Study Day 0) and at Weeks 14 and 28, resulting in data collection at Baseline and at Weeks 8, 16, 24, 38, and 52. The clinical reviewer noted that mean values for the vital signs were similar across both treatment groups and the changes from baseline was small for all time points throughout the studies for systolic blood pressure, diastolic blood pressure, heart rate, temperature, and respiratory rate.

9. Advisory Committee Meeting

HZT-501 is a combination product that includes ibuprofen, 800 mg, and famotidine, 26.6 mg. Both of the components of this combination product are approved and widely available over-the-counter. There were no new or unique concerns identified during the review of this product compared to each component of the combination product. Therefore, no advisory committee meeting was convened for this product.

10. Pediatrics

The Pediatric Research Equity Act (Public law 108-155) (PREA) requires new drug applications (NDAs) and biologics licensing applications (BLAs) (or supplements to applications) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration to contain a pediatric assessment unless the applicant has obtained a waiver or deferral (see section 505B(a) of the Act). Therefore, PREA was triggered for this application because this product includes both a new indication and new dosage form for both ibuprofen and famotidine, and a new dosing regimen for famotidine.

[REDACTED] (b) (4)

A Pediatric and Maternal Health Staff (PMHS) consult was requested to review the plan to allow a [REDACTED] (b) (4)

[REDACTED] Additionally, ibuprofen use data were obtained through a consult from the Office of Surveillance and Epidemiology (OSE) Division of Epidemiology. The reader is referred to the PMHS consult by A. Karesh, dated December 14, 2010, for complete information. Current labeling indications for pediatric use of ibuprofen include the relief of signs and symptoms of juvenile idiopathic arthritis (JIA) for which chronic use is likely. JIA is a condition that affects both children and adults, but JIA is extremely uncommon in patients less than 2 years of age. Therefore, studies in children less than two years of age would be highly impractical. Other labeled pediatric indications for ibuprofen include for fever reduction and relief of mild to moderate pain. Both of these indications include children from 6 months to 2 years of age. However, chronic use is unlikely for these indications and

therefore, HZT-501 is not likely to be used for these indications. Thus, the recommendation to waive studies for patients birth to 2 years of age was based on the pediatric JIA population, as this population was most likely to use ibuprofen chronically and be at increased risk for the development of GI ulcers. Based on this information, as well as the recommendations of the PMHS review and use data obtained from the OSE review, the recommendation for studies to be required by the applicant under PREA was amended to include studies in pediatric patients down to 2 years of age. These pediatric studies that would be required of the applicant were developed and presented to the Pediatric Research Committee (PeRC) on December 8, 2010. The committee found that pediatric studies recommended by the Division to be acceptable and agreed that the following studies be performed as postmarketing studies required by section 505B(a) of the Federal Food, Drug, And Cosmetic Act.

1. Development of an age appropriate formulation of ibuprofen/famotidine to be used in pediatric patients.
2. A study to characterize ibuprofen and famotidine pharmacokinetic (PK) parameters following administration of a single dose of a new formulation (suspension) of ibuprofen/famotidine combination in healthy human subjects. PK endpoints must include PK parameters for both ibuprofen and famotidine such as C_T , C_{max} , T_{max} , AUC, $T_{1/2}$, clearance, and $V_{d_{ss}}$, as applicable.
3. A study to evaluate the pharmacokinetics (PK) and safety of HZT-501 in children and adolescents ages 10 years through 16 years, 11 months of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 10 years to 16 years, 11 months.
4. A study to evaluate the pharmacokinetics (PK) and safety of an age appropriate formulation of ibuprofen/famotidine to be used in children and adolescents ages 2 years through 10 years of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 2 years to 10 years.

These PREA postmarketing studies were sent to the applicant for review and concurrence.

11. Other Relevant Regulatory Issues

A. Financial disclosures

The applicant reported that 894 investigators participated in the phase 3 trials. Of these 894 investigators, the applicant received financial disclosure information on all but 3 of the investigators. These three investigators (one each from site 165, site 152, and site 329) were removed as investigators from the clinical trials. The applicant provided a signed copy of FDA Form 3454 certifying that they have not entered into any financial arrangements with the remaining 891 clinical investigators, whereby the value of compensation to the investigator

could be affected by the outcome of the study as defined in 21 CFR 54.2(a). In addition, none of the investigators disclosed any proprietary interest in Duexis or any significant equity interest in Horizon Therapeutics, Inc. as defined in 21 CFR 54.2(b). Finally, no investigator was the recipient of significant payments as defined in 21 CFR 54.2 (f).

B. DSI audits

The reader is referred to the Division of Scientific Investigations (DSI) review by K. Malek, dated April 8, 2011 for complete details.

All of the sites that enrolled patients in the phase 3 studies were domestic. Three clinical sites were initially chosen for DSI inspection; site 144 (study 301), Leann Serbousek, M.D., Oklahoma City, OK, 38 patients; and site 180 (study 301), William Abraham, M.D., Tucson, AZ, 22 patients; and site 389 (study 303), Vaughn Mancha, M.D., Montgomery, AL, 167 patients). These sites were chosen based on the total number of patients enrolled. Additionally, site 180 was inspected because there appeared to be a higher rate of ulcers in the placebo group compared to other sites.

The DSI inspections for site 144 and site 180 found no deviations from regulations and were classified as No Action Indicated (NAI). Therefore, the DSI reviewer concluded that data from these two sites appeared valid and could be used in support of the NDA. However, the DSI inspection for site 389 uncovered significant deficiencies including the following:

1. Failure to ensure that the investigation was conducted according to the investigational plan
2. Failure to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation

Under each of these deficiencies, the DSI investigator noted numerous examples of the investigator's failure to comply. As a result of these deficiencies, the investigator was issued a Warning Letter on February 17, 2011. Furthermore, the DSI reviewer concluded that the study was not conducted adequately at site 389, and that data generated from this site should not be used in support of the of the NDA. Based on the information received from DSI regarding site 389, two additional DSI inspections for study 303 were requested because this finding called in to question the conduct of the applicant in providing adequate oversight of the individual sites, as well as the possibility that other sites participating in 303 may have had significant deficiencies relating to study conduct.

Additionally, the review division questioned the conduct of study 303 based on the findings of the inspection at site 389 and felt that additional information to establish the validity of the results from study 303 was necessary. Therefore, the review division requested additional DSI inspections at two additional sites (site 340, Vrijendra Kumar, Las Vegas, NV, 35 patients; and site 363, Dennis Riff, Anaheim, CA, 76 patients), as well as an inspection of Horizon Pharma, Inc. to ensure that the applicant had provided proper oversight for the clinical trials. The two

additional study sites for study 303 were requested because these sites had large number of patients who were terminated the study early. Late in the review cycle, results of the DSI inspection at site 363 uncovered additional deficiencies that called the validity of the data in four patients into question (patient 005,021,050, and 100). The DSI reviewer recommended that these four patients also be excluded from all efficacy analyses. The inspection at Horizon Pharma, Inc. did not uncover any substantive deficiencies. Therefore, overall, the reviewer concluded that clinical study reviewed from study 303 (with the exception of 4 patients from site 363, and 167 patients from site 389) were valid and could be reviewed.

C. Clinical consults

To assist in the development of appropriate pediatric studies required under PREA, consults were obtained from the PMHS staff (see review by A. Karesh for complete details), and from OSE, Division of Epidemiology (see review by P. Greene for complete details). Additionally, standard consults were obtained from DDMAC, DMEPA, and SEALD to review product labeling.

12. Labeling

Proprietary name

During this review cycle, the originally proposed trade name of (b) (4) was submitted for review. A review of the trade name was performed by L. Pincock in the Division of Medication Errors Prevention and Analysis (DMEPA). The proposed name, (b) (4), was rejected by DMEPA (b) (4)

The applicant subsequently submitted a new proposed name, Duexis. A review of this trade name was performed by Y. Maslov, DMEPA. The trade name, Duexis, was found to be acceptable.

Physician labeling

Final labeling for the product was satisfactorily negotiated during the review cycle. The final labeling conforms to the Physician Labeling Rule (PLR) format. The reader is referred to final labeling for the product for complete details. Highlights of final labeling for Duexis are presented below.

Boxed Warning

A boxed warning will be included as is required for all NSAID products to warn of the risk of serious cardiovascular and gastrointestinal events. Serious cardiovascular events include myocardial infarction, and stroke, which can be fatal. Serious gastrointestinal events include bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.

Section 1: Indications and usage

The indications section will state specific approved indications for ibuprofen, and describe the reduction of risk of upper gastrointestinal ulcers for the famotidine component, as shown below:

“DUEXIS, a combination of the NSAID ibuprofen and the histamine H₂-receptor antagonist famotidine, is indicated for the relief of signs and symptoms of rheumatoid arthritis and osteoarthritis and to decrease the risk of developing upper gastrointestinal ulcers, which in the clinical trials was defined as a gastric and/or duodenal ulcer, in patients who are taking ibuprofen for those indications. The clinical trials primarily enrolled patients less than 65 years of age without a prior history of gastrointestinal ulcer. Controlled trials do not extend beyond 6 months.”

Section 5: Warnings and Precautions

This section was written to incorporate specific warnings and precautions that have been previously included in the labeling for both ibuprofen and famotidine. This section includes the following specific warnings and precautions: cardiovascular thrombotic events; hypertension; congestive heart failure and edema; risk of gastrointestinal ulceration, bleeding, and perforation; active bleeding; renal injury; seizures; anaphylaxis; skin reactions; pregnancy; hepatic injury; anemia; inhibition of platelet aggregation; pre-existing asthma; concomitant NSAID use; aseptic meningitis; corticosteroid treatment; masking of inflammation and fever; and visual disturbances.

Section 6: Adverse Reactions

This section will relate the adverse reactions of ibuprofen and famotidine. Additionally, adverse reaction observed in the clinical trials for HZT-501 will also be presented.

Specific additional language reporting the development of acute renal failure will be included, as well as the incidence of elevations in serum creatinine during the study.

Section 8: Use in Special Populations

The section will include special information for patients with renal insufficiency. Additional language stating that patients with creatinine clearance <50 mL/min should not take Duexis is included because the product is a fixed dose combination and, therefore, the dose cannot be adjusted appropriately for patients with severe renal insufficiency. Additionally, careful language regarding the limitation of data in patients 65 years of age and older were added with a cross-reference to section 14, Clinical Studies.

Section 12: Clinical Pharmacology

This section will discuss the effects of food on absorption of HZT-501. It appears that intake of a high fat diet did not change the PK parameters significantly. However, this information was not placed in dosage and administration because ibuprofen labeling states that it should be taken with food if stomach upset occurs.

Section 14: Clinical Studies

This section will include information from the phase 3 clinical trials. As stated above, the analyses to be used for labeling will be the overall incidence rate analyses only. Additional information about the results in patients at higher risk (i.e., patients taking low-dose aspirin, patients 65 years of age and older, and patients with a prior history of gastrointestinal ulcer) were also included in this section.

Carton and immediate container labels

The carton and container labels were revised as recommended in the DMEPA review.

Patient labeling/Medication guide (if considered or required)

Please see the Division of Risk Management review by L. Ford, dated March 23, 2011 for complete details.

The patient labeling and medication guide were reviewed and changes were made based on input from DRISK.

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

The application has been reviewed by all relevant disciplines, all of whom recommend an approval action. I agree with the recommendations from each discipline. Therefore, I recommend that an Approval action be taken for this application with postmarketing requirement studies to be performed as triggered by PREA and described below.

Risk Benefit Assessment

The benefit of HZT-501 in the reduction of the risk of ibuprofen-associated gastric ulcers in patients who require treatment with ibuprofen appears to have been demonstrated based on the data submitted by the applicant. The crude incidence rates for the development of gastric ulcers in study 303 were 15.4% lower in the HZT-501 treatment group compared to patients who received ibuprofen, and this result was highly statistically significant ($p = 0.0001$). Furthermore, this difference in incidence of ulcers between the HZT-501 treatment group and the ibuprofen treatment group is in the range seen with PPIs approved for the reduction of risk of NSAID-associated gastric ulcers. One concern with the statistical reviewer is the weakness of study 301. Study 301 failed to reach statistical significance based on the crude incident rate analysis if all early terminated patients were counted as treatment failures; the most conservative analysis. I agree with the clinical and statistical reviewer that study 301 is not persuasive when analyzed using the most conservative analysis. However, based on the SPA agreement for study 301, the applicant's pre-specified primary endpoint analysis using the pre-specified analysis population demonstrates a statistically significant result. Given the presence of the SPA agreement and the demonstration of a statistically significant effect using the pre-specified analysis plan in the pre-specified analysis population for both upper gastrointestinal and gastric ulcers, final labeling could reasonably include an indication for risk reduction of upper gastrointestinal ulcers.

As stated in my discussion of efficacy in Section 7, the applicant is seeking an indication that includes all gastrointestinal ulcers (gastric and duodenal). I agree that using the pre-specified statistical analysis method with the pre-specified analysis population as agreed upon in the SPA that the applicant has demonstrated a statistically significant treatment effect for HZT-501. Therefore, it is acceptable to provide this information in product labeling. However, the applicant did not provide convincing evidence of the effect of HZT-501 in preventing duodenal ulcers. *H. pylori* testing was not performed in patients who developed duodenal ulcers, and it is possible that some of these patients developed *H. pylori* infection as the cause of the duodenal ulcers. Furthermore, the duodenal ulcer rates were low in both studies, making clear conclusions difficult to draw despite the statistically significant difference observed in study 303. In other products approved for the risk reduction of NSAID-associated ulcers, none of the other products have been approved for risk reduction of duodenal ulcers. Therefore, I recommend that the applicant receive only the indication for the risk reduction of NSAID-associated upper gastrointestinal (gastric and duodenal) ulcers, labeling for duodenal ulcers should not be included. It may appear inconsistent that upper gastrointestinal ulcers can be indicated while duodenal ulcers would not. This apparent inconsistency is based mostly on the factors described above that limit the ability to draw a clear conclusion about treatment effect for duodenal ulcers specifically. Therefore, it is not entirely inconsistent to agree to use of the upper gastrointestinal ulcer endpoint in labeling because it is not a single endpoint, but rather a combination of the incidence of both gastric and duodenal ulcers. ..

A major limitation in the data submitted are the small numbers of patients studied in clinical trials that were at high risk for development of gastrointestinal ulcers (e.g., patients over 65 years of age, patients taking concomitant low-dose aspirin, and patients with a prior history of gastrointestinal ulcers). Approximately 18% of the patients in the study were taking low-dose aspirin, and in this subgroup, the effect of HZT-501 appeared to provide benefit (9% decrease in incidence of gastric ulcers compared to ibuprofen), but this sub-group analysis was performed post-hoc, and the population was small. Furthermore, sub-group analyses for patients ≥ 65 years of age or with a history of previous gastrointestinal ulcer failed to show any benefit in the effect of HZT-501 compared to ibuprofen alone. Again, these analyses were performed post-hoc and evaluated small numbers of patients. Nevertheless, given the failure to demonstrate at least a similar treatment effect in patients 65 years of age and older and in patients with a prior history of upper gastrointestinal ulcers compared to the overall study results, the product should clearly indicate the limitations of the study and that these populations were not studied adequately.

The safety of the product was also reviewed and is generally acceptable. Additional labeling to describe cases of acute renal failure and increases in serum creatinine should be included based on data reviewed from the clinical trials. Additionally, the labeling should also include specific recommendation that the product should not be used in patients with moderate to severe chronic kidney disease (GFR<50 cc/min) because the tablet cannot be split and the dosing interval cannot be changed to account for the requirement to decrease famotidine dose or dose interval in patients with GFR<50 cc/min).

Additionally, I agree with the recommendation for post-marketing studies under PREA to evaluate the effect of HZT-501 in pediatric patients that may require longer term ibuprofen

because there are substantial numbers of pediatric patients that have been prescribed ibuprofen, and pediatric patients are also susceptible to the gastrointestinal complications of ibuprofen and other NSAIDs.

In summary, the risk benefit profile of HZT-501 in the reduction of risk of ibuprofen-associated upper gastrointestinal ulcers is generally favorable, and I recommend that an Approval action be taken for the application.

Recommendation for Postmarketing Risk Evaluation and Management Strategies

No special postmarketing risk management activities are recommended for this application.

Recommendation for other Postmarketing Requirements and Commitments

The following postmarketing requirement studies triggered by PREA were negotiated during this review cycle and include the following:

1. Development of an age appropriate formulation of ibuprofen/famotidine to be used in pediatric patients.

Final Protocol Submission: July, 2013
Study Completion Date: July, 2015
Final Report Submission: March, 2016

2. A study to characterize ibuprofen and famotidine pharmacokinetic (PK) parameters following administration of a single dose of a new formulation (suspension) of ibuprofen/famotidine combination in healthy human subjects. PK endpoints must include PK parameters for both ibuprofen and famotidine such as C_T , C_{max} , T_{max} , AUC, $T_{1/2}$, clearance, and $V_{d_{ss}}$, as applicable.

Final Protocol Submission: July, 2016
Study Completion Date: December, 2016
Final Report Submission: March, 2017

3. A study to evaluate the pharmacokinetics (PK) and safety of HZT-501 in children and adolescents ages 10 years through 16 years, 11 months of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 10 years to 16 years, 11 months.

Final Protocol Submission: October, 2011
Study Completion Date: October, 2013
Final Report Submission: May, 2014

4. A study to evaluate the pharmacokinetics (PK) and safety of an age appropriate formulation of ibuprofen/famotidine to be used in children and adolescents ages 2 years through 9 years 11 months of age who require chronic treatment with NSAIDs. The pediatric study will be a 6-month (24-week), multicenter, open-label study to evaluate the safety of DUEXIS in children and adolescents ages 2 years to 9 years 11 months of age.

Cross Discipline Team Leader Review

Final Protocol Submission: January 2016

Study Completion Date: January 2018

Final Report Submission: July 2018

Recommended Comments to Applicant

None.

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

/s/

LYNNE P YAO
04/22/2011
CDTL memo