dosing. ●The differences between the TID and BID dosing regimens were more marked in the normal weight (BMI 20-25 kg/m^2) subjects. ●Trough plasma FAM concentrations on Day 5 were the same for TID and BID dosing. ●Both TID and BID dosing with FAM were well tolerated by all subjects. **Conclusions:** TID oral administration of an 80-mg total daily dose of FAM produced better gastric acid suppression and better maintenance of gastric pH above a pH 2.5 threshold than did administration of the same total daily dose on a BID basis, without leading to FAM accumulation.

	Median 24-hr pH (Day 1)					
	All Subjects (N=13)		Upright Position (N=13)		Normal Weight Subjects (N=9)	
	BID	TID	BID	TID	BID	TID
Mean	3.52	3.63	3.38	3.79	3.33	3.78
SD	1.1	0.7	1.2	0.8	1.0	0.7
Range	1.8-5.1	2.5-4.5	1.8-5.2	2.3-4.7	1.8-4.8	2.5-4.5

T1972

Pharmacokinetics of Naproxen and Esomeprazole in PN400, a Single-Tablet, Multilayer Formulation of Enteric-Coated Naproxen Coupled with Immediate-Release Esomeprazole

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Introduction: PN400 is a single-tablet formulation with an enteric-coated (EC) naproxen core surrounded by an immediate-release (IR) esomeprazole mantle designed for initial and rapid release of esomeprazole in the stomach followed by release of EC naproxen after esomeprazole absorption. The aim of this study was to determine levels of exposure of esomeprazole and naproxen when used in combination in PN400 and with EC esomeprazole + naproxen 500 mg. Methods: This randomized, open-label, 9-day, 4-way crossover, single-center study enrolled 28 healthy *H. pylori*-negative adults without a history of peptic ulcer/acid-related gastrointestinal symptoms. Subjects were randomized to different sequences of the following: A) PN400/E30 [EC naproxen 500 mg/IR esomeprazole 30 mg] BID; B) PN400/E20 [EC naproxen 500 mg/IR esomeprazole 20 mg] BID; C) PN400/E10 [EC naproxen 500 mg/IR esomeprazole 10 mg]; and D) EC E20 [EC esomeprazole 20 mg] QD + non-EC naproxen 500 mg BID. Blood samples were taken on Days 1 and 9 before dosing and at various times up to 24 hours afterwards for pharmacokinetic assessments of esomeprazole and naproxen. Results: Esomeprazole was rapidly absorbed from all 3 doses of PN400 with measurable plasma concentrations as early as 10 minutes after the AM dose and at 20-30 minutes after the PM dose. Differences in Cmax and AUCs for esomeprazole from PN400 were generally dose-dependent. As expected, the Tmax for EC naproxen was delayed in relation to the Tmax for esomeprazole. Steady-state AUCs for naproxen monocomponent were comparable to all PN400 formulations. Tmax with non-EC naproxen occurred considerably earlier than with the EC naproxen component of the PN400 formulations. Esomeprazole and naproxen pharmacokinetic parameters for the AM dose on Day 9 of BID dosing for PN400 are provided in the table. Conclusion: PN400 produced dose-dependent increases in plasma esomeprazole concentrations and similar naproxen concentrations to dosing with EC E20 + naproxen. The pharmacokinetics of esomeprazole administered as the PN400 formulation were consistent with immediate release, and Tmax for esomeprazole preceded that for EC naproxen.

		Esomeprazole			Naproxen	
	C_{max}, ng/mL	T_{max}, hr	$AUC_{0\text{-}10AM}$, hr*ng/mL	C_{max}, mcg/mL	T_{max}, hr	$AUC_{0\text{-}10AM}$, hr*mcg/mL
PN400/E30	1584 (39)	0.50 (0.17-1.50)	2779 (45)	80.9 (23)	3.00 (0.00-8.00)	603 (21)
PN400/E20	715 (52)	0.50 (0.17-1.50)	1216 (69)	86.2 (22)	3.00 (0.00-8.05)	607 (19)
PN400/E10	278 (57)	0.33 (0.17-1.00)	368 (89)	87.1 (21)	2.50 (0.00-8.00)	637 (17)
EC E20 + naproxen	435 (48)	1.50 (1.00-14.00)	1046 (54)	90.0 (19)	1.50 (0.50-4.00)	617 (12)

Values are mean (% coefficient of variation) for C_{max} and AUC, and median (range) for T_{max}.

T1973

Diagnostic Precision of Primary Care Electronic Database for Study of Gastrointestinal Bleeding and Its Ability to Detect the Influence of Aspirin

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INTRODUCTION: Large Primary Care electronic databases offer good opportunities for systematic epidemiological research. However, general practitioners do not necessarily code events in the same way as Hospital Events Statistics do. We, therefore, investigated the extent to which coding influences recorded gastrointestinal (GI) bleeding event rates using QRESEARCH, a new larger electronic database. AIMS & METHODS: Patients were included in the analysis if they were aged 45-100 years and had at least twelve months of electronic health records and were registered with a participating practice at any time between 1 April 2003 and 31 March 2007. All codes with mention of gastrointestinal bleeding were extracted and summarised to produce eight categories, as in the Table. RESULTS: Four hundred and fifty nine practices met inclusion criteria to generate 4.87 million person years of observation. Over 99% of aspirin use was for ≤300mg per day. As shown in the Table, high rates were recorded for upper gastrointestinal bleeding and rectal bleeding/melena, whilst specific ulcer bleeding was under recorded. Nevertheless, the study was able to detect a 1.58 (1.45-1.71) fold hazard ratio for upper gastrointestinal bleeding and a 1.47 (1.42-1.52) hazard ratio for rectal bleeding / melena, related to aspirin use. CONCLUSION: Coding imprecision limits the exactitude of conclusions but is not enough to obscure the impact of aspirin on event rates. The impact of aspirin is likely to be higher when coding and exposure imprecisions are allowed for.

	Broad Term	Rate/100,000	Specific Term	Rate/100,000
Ulcer bleeding	All specific ulcer bleeding	6.25	Not haemorrhagic gastritis	6.17
Upper GI bleeding	All upper GI bleeding	72.3	With ulcer code and nil lower	3.77
Rectal bleeding/melena	All melaena/rectal bleeding	564	No lower GI code	564
Any GI bleeding	All GI bleeding	5.49	No lower GI code	5.49

T1974

HZT-501, A Novel Combination of Ibuprofen (Ibu) and Famotidine (FAM), Provides Pharmacokinetics Comparable to That of Commercially Available Ibu and Fam in a Patient-Friendly Dosing Form: Evaluation in Healthy and Renally-Impaired Subjects

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Background: Clinical studies have demonstrated that reducing gastric acid secretion with FAM during treatment with non-steroidal anti-inflammatory drugs (NSAIDs) decreases the risk of development of upper gastrointestinal (GI) ulceration. However, physician compliance is reported to be <30% in co-prescribing acid-reducing agents for patients on NSAIDs, and patient compliance with the differing dosing regimens for these various agents is reported to be only 37%. HZT 501, a combination product containing IBU 800 mg and FAM 26.6 mg, is designed both to improve patient compliance and to ensure that the time of gastric acid suppression coincides with the time of maximum vulnerability to NSAID-induced GI ulceration. **Objective:** To evaluate the bioequivalence of HZT-501 and concurrent administration of equivalent doses of commercially available IBU and FAM in healthy subjects and in subjects with renal impairment. **Methods:** Randomized, open-label, single-dose, 2-period crossover study in 24 healthy subjects and 5 subjects with moderate-to-severe renal impairment (creatinine clearance < 45 mL/min [Cockroft-Gault formula]). Oral administration of HZT-501, and concurrent oral administration of IBU 800 mg and FAM 26.6 mg, in two treatment periods separated by at least a 1-week washout. Blood samples collected for pharmacokinetics (PK) analysis during the 24 (healthy subjects) or 48 (subjects with renal impairment) hr after dosing. Safety assessed in all subjects. **Results:** There were no statistically significant sequence, period, or formulation effects in healthy subjects for either plasma concentrations or computed PK parameters for either IBU or FAM when administered via HZT 501 or via concurrent administration of commercially available IBU and FAM. The following table shows the PK parameters for both formulations in healthy and renally-impaired subjects. Both HZT-501 and concurrent administration of FAM and IBU were well tolerated by healthy and renally-impaired subjects. **Conclusions:** Oral administration of HZT-501 to healthy subjects is bioequivalent to concurrent oral administration of equivalent doses of commercially available IBU and FAM. HZT-501 is designed for administration on a three-times-per-day dosing schedule.

Parameter	IBU				FAM			
	Healthy (N=20)		Renally-Impaired (N=5)		Healthy (N=20)		Renally-Impaired (N=5)	
	HZT-501	Motrin	HZT-501	Motrin	HZT-501	Motrin	HZT-501	Motrin
t_{max} (hr)	1.5± 0.6	1.4± 0.7	2.1± 1.3	2.5± 3.1	2.1± 0.8	2.3± 0.9	5.3± 2.1	3.6± 1.5
C_{max} [1]	67± 18	70± 19	45± 25	48± 21	163± 53	182± 63	110± 45	101± 40
$t_{1/2}$ (hr)	2.3± 0.4	2.2± 0.4	2.5± 0.9	2.6± 1.0	3.2± 0.8	3.5± 1.1	11.4± 3.2	13.6± 6.3
AUC [2]	232± 61	232± 61	178± 98	198± 80	993± 342	1046± 320	1674± 689	1790± 951

[1] µgmL for IBU; ng/mL for FAM [2] µg●hr/mL for IBU; ng●hr/mL for FAM

T1975

NSAIDs: A Direct Activator of Acid Secretion in Parietal Cells

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are one of the most widely used classes of drugs in the treatment of inflammatory and degenerative conditions. The side effects of NSAIDs, particularly the increased risk of gastrointestinal and renal complications, have caused concern in their widespread use. NSAID use increases the risk of peptic ulcer disease (PUD), particularly with prolonged duration of therapy or higher dose. Studies have demonstrated a key inhibitory role of NSAIDs in the cyclooxygenase pathway leading to inhibition of prostaglandin synthesis, an important mediator in the protection of gastrointestinal mucosal lining. Little is known, however, about the effect of NSAIDs directly on the parietal cell. This study aims to investigate the effect of NSAIDs on acid secretion in the parietal cell. **Methods:** Rats were fasted for 12-18 hrs prior to sacrifice to ensure basal acid secretion. Gastric glands were hand-dissected from the corpus, transferred to a coverslip, and placed onto a thermostatically-controlled chamber. The chamber was mounted on a microscope attached to a digital imaging system. The glands were incubated with the pH-sensitive dye BCECF. Intracellular pH (pH_i) changes were monitored using real-time video imaging. Data were collected as arbitrary intensity units every 15s and converted to absolute