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J Clin Pharmacol 2006 46: 855

DOI: 10.1177/0091270006289848

Pharmacokinetic Interactions of Concomitant Administration of Febuxostat and NSAIDs

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To evaluate the effect of febuxostat on the pharmacokinetics of indomethacin and naproxen and vice versa, 2 multiple-dose, 3-period crossover studies were performed in healthy subjects. In study 1, subjects received febuxostat 80 mg once daily, indomethacin 50 mg twice daily, or both. In study 2, subjects received febuxostat 80 mg, naproxen 500 mg twice daily, or both. Twenty-four-hour blood samples were collected on day 5 in study 1 and day 7 in study 2. In study 1, 90% confidence intervals of geometric mean ratios for maximum plasma concentration (C_{max}) and area under the curve (AUC) were within the 0.80 to 1.25 no-effect range for febuxostat and indomethacin. In study 2, 90% confidence intervals for febuxostat C_{max} and AUC extended above that range, with increases of 28% and 40% in C_{max} and AUC_{24}, respectively. However, 90% confidence intervals for naproxen C_{max} and AUC were within the 0.80 to 1.25 range. Febuxostat had no effect on the plasma pharmacokinetics of indomethacin and naproxen. Similarly, indomethacin had no effect on the plasma pharmacokinetics of febuxostat. Although naproxen caused an increase in plasma exposure to febuxostat, this increase is not expected to be clinically significant. Therefore, based on the plasma pharmacokinetic data in healthy subjects, febuxostat may be administered with indomethacin or naproxen with no dose adjustments for febuxostat, indomethacin, or naproxen.

Keywords: *Febuxostat; drug-drug interaction; NSAID; indomethacin; naproxen; pharmacokinetics*

Journal of Clinical Pharmacology, 2006;46:855-866

Gout is the most common form of inflammatory arthritis in men older than 40 years and is characterized by recurrent attacks of acute inflammation in 1 or more joints because of deposition of monosodium urate crystals in the joint cavity.[1,2] Elevated serum concentrations of uric acid (hyperuricemia) are seen in more than 90% of patients with gout, and hyperuricemia is considered the precursor of gout.[1] The condition generally occurs after years of sustained hyperuricemia, and a clear relationship between serum uric acid and the risk of developing gout has been demonstrated.[1,3] According to the most recent National Health and Nutrition Examination Survey (NHANES III), gout is estimated to affect approximately 5.1 million people in the United States, and its prevalence is increasing rapidly because of an increase in 2 important risk factors of hyperuricemia: aging and obesity.[4,5]

The 2 important cornerstones of gout management are (1) management or control of hyperuricemia and (2) treatment or prevention of acute attacks of gout.[6] Management or control of hyperuricemia in gout involves inhibitors of xanthine oxidase, uricosuric agents, or uricase. These agents lower uric acid concentrations in serum by inhibiting production of uric acid (ie, inhibitors of xanthine oxidase) or by increasing clearance of uric acid from the body (ie, uricosurics or uricase). In the United States, inhibitors of xanthine oxidase are the most widely prescribed category of drugs for hyperuricemia management in patients with gout. For treatment or prevention of acute gout attacks (including those caused by the initiation of antihyperuricemic therapy), 3 categories of drugs commonly have been used: antimitotics (eg, colchicine), nonsteroidal anti-inflammatory drugs (NSAIDs), and systemic steroids (eg, prednisone).[6] Because of the adverse events associated with colchicine therapy, NSAIDs (eg, indomethacin and naproxen), where they are not contraindicated, are the drugs of choice in treating or preventing acute

From TAP Pharmaceutical Products, Inc, Lake Forest, Illinois. Funded by TAP Pharmaceutical Products, Inc. Presented in part at the 69th annual scientific meeting of the American College of Rheumatology (November 2005). Submitted for publication December 16, 2005; revised version accepted April 11, 2006.

DOI: 10.1177/0091270006289848

attacks of gout. Systemic steroids are recommended only when patients do not respond to colchicine or NSAIDs or when colchicine or NSAIDs are contraindicated.

Febuxostat (2-[3-cyano-4-(2-methylpropoxy)-phenyl] -4-methylthiazole-5-carboxylic acid) is a potent novel nonpurine selective inhibitor of xanthine oxidase (NP-SIXO) and was shown to have great efficacy in lowering serum uric acid concentrations in animals.[7-11] Results of phase I, II, and III studies in healthy subjects and subjects with hyperuricemia associated with gout have confirmed the ability of febuxostat to reduce serum uric acid concentrations in humans in a dose-dependent manner.[12-15] In healthy human subjects, orally administered febuxostat is rapidly absorbed with the time to reach the observed maximum plasma concentration (t_{max}) of approximately 1 hour. The drug is highly bound to albumin in blood (~99%) and appears to have a low to medium apparent volume of distribution at steady state of approximately 0.7 L/kg. Febuxostat is metabolized mainly to its acyl-glucuronide metabolite (via uridine diphosphoglucuronosyltransferases [UGT] 1A1, 1A3, 1A7, 1A8, 1A9, 1A10, and 2B7; unpublished data) and, to a lesser extent, its active oxidative metabolites (via cytochrome P-450 1A1, 1A2, 2C8, and 2C9; unpublished data).[16-18] Approximately 33% and 11% of the orally administered dose is recovered in urine as the acyl-glucuronide of febuxostat and as the oxidative metabolites and their glucuronide conjugates, respectively.[18] Only a small fraction (< 2%) of the orally administered dose was excreted renally as unchanged febuxostat, indicating that renal elimination plays a minor role in the elimination of febuxostat from the body.[18]

During initiation of antihyperuricemic therapy, a rapid decrease in serum uric acid concentrations may precipitate an acute attack of gout. Therefore, febuxostat may need to be administered with NSAIDs such as indomethacin or naproxen. Similar to febuxostat, indomethacin and naproxen also undergo glucuronidation and are highly protein bound.[19-24] According to the literature, probenecid, a uricosuric agent, inhibits the glucuronidation of both indomethacin and naproxen.[25,26] In addition, results of in vitro and in vivo studies have shown that naproxen and/or indomethacin themselves may cause inhibition of the glucuronidation of other drugs.[27-29] Therefore, we decided to investigate the effect of febuxostat on the pharmacokinetics of indomethacin and naproxen and vice versa.

METHODS

Subjects

Two studies were conducted to investigate the effect of febuxostat on the pharmacokinetics of indomethacin and naproxen and vice versa. Enrollment for both studies started after investigational review board (Quorum Review Inc; Seattle, Wash) approval. Eligible healthy male and female subjects between 18 and 55 years of age, inclusive, were allowed to enroll in each study after signed informed consent was obtained. Subjects were required to have a body mass index less than 30 kg/m^2, a normal serum creatinine level, no history of drug sensitivity or allergic reaction to any drug, no hypersensitivity to aspirin and NSAIDs, and no comorbid, uncontrolled metabolic or psychiatric conditions. Exclusion criteria included a diagnosis of gout, a history of xanthinuria or recurrent gastrointestinal lesions, evidence of occult blood in stool, clinically significant abnormal laboratory test or electrocardiographic results, a concurrent disease state that required long-term daily medication, a history of cancer with less than 5 years of remission, and positive test results for hepatitis B, hepatitis C, or human immunodeficiency virus antibody. In addition, subjects were excluded from the study if they had taken any over-the-counter or prescription medication within 1 and 4 weeks, respectively, of the initial dose of study drug; used tobacco or other nicotine-containing products within 3 months before the initial dose of study drug; or had a history of alcohol or drug abuse. Female subjects were excluded from the study if they were pregnant or breastfeeding. Both studies were conducted at Seaview Research, Inc (Miami, Fla).

Experimental Design

Both studies were phase I, single-center, open-label, multiple-dose, randomized, 3-period crossover studies. In each study, an attempt was made to enroll equal numbers of subjects of each sex. Subjects were assigned randomly to 1 of 3 regimen sequences, as shown in Figure 1.

During confinement to the testing facility, subjects abstained from all food and beverage except for scheduled meals provided by the testing facility. Caffeine, alcohol, high-purine foods, and grapefruit and grapefruit juice were not to be consumed. Subjects were instructed to abstain from eating high-purine foods a week before confinement. During confinement, all

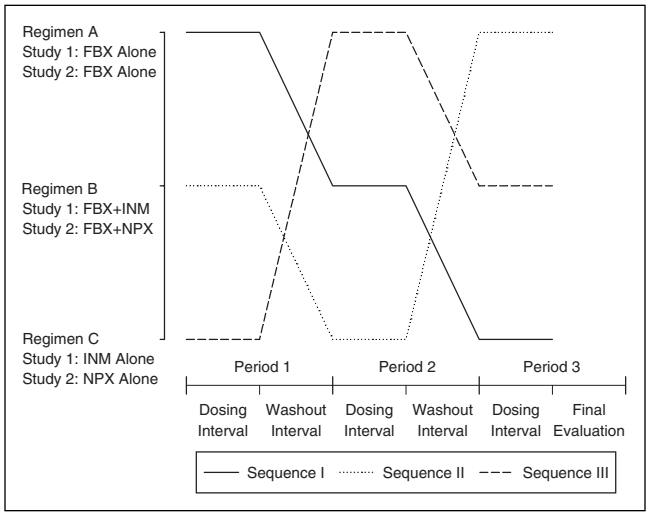

Figure 1. Diagram of regimen orders for sequences I, II, and III in studies 1 and 2. FBX, febuxostat 80 mg once daily; INM, indomethacin 50 mg twice daily; NPX, naproxen 500 mg twice daily. Dosing interval: 5 days in study 1 and 7 days in study 2. Washout interval: 2 days in study 1 and 7 days in study 2. Final evaluation: the day after the dosing interval in period 3 in studies 1 and 2 for subjects who completed the study.

subjects were served meals relative to the time of dosing with approximate times of breakfast at 0730 hours, lunch at 1300 hours, dinner at 1800 hours, and an evening snack at 1930 hours. Breakfast and snack were to be finished within 30 minutes. No food was allowed from 2000 hours until 0730 hours the next morning. Water was allowed as desired except 1 hour before and 1 hour after drug administration.

In study 1, subjects were confined to the testing facility and supervised for approximately 21 consecutive days. Confinement began at approximately 1100 hours on day –1 of period 1 to obtain all the necessary laboratory test results and ended when all study procedures were completed on day 6 of period 3. On dosing days, days 1 to 5 of each period (ie, dosing interval; Figure 1), the doses were administered according to the regimen assigned for the period. For regimen A, four 20-mg tablets of febuxostat were administered at 0800 hours with 240 mL of water. For regimen B, four 20-mg tablets of febuxostat and a single 50-mg capsule of indomethacin were administered at 0800 hours with 240 mL of water. A single 50-mg capsule of indomethacin was administered at 2000 hours with 240 mL of water. For regimen C, a single 50-mg capsule of indomethacin was administered at 0800 hours and at 2000 hours with 240 mL of water. There were 2 days between the last dose in a period and the first dose of the subsequent period when no doses were administered (ie, washout interval; Figure 1). However, subjects remained confined on these days. On days 1 through 5 of each period, venous blood samples were collected within 5 minutes before the morning administration of study drugs for the determination of febuxostat and/or indomethacin concentrations in plasma. On day 5 of regimens A and B, venous blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and 24 hours after the morning administration of febuxostat for the determination of febuxostat in plasma. Venous blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 12.25, 12.5, 13, 13.5, 14, 15, 16, 18, and 24 hours after the day 5 morning administration of indomethacin in regimens B and C for the determination of indomethacin concentrations in plasma. On day 6 of period 3, final study procedures were conducted after the 24-hour sample was obtained. Blood samples also were obtained for clinical laboratory testing (eg, hematology/serum chemistry) at screening and days –1 and 6 of each period for subjects who completed the study.

In study 2, subjects were confined to the testing facility and supervised for approximately 9 days in each period. Confinement began for each period at approximately 1100 hours on day –1 and ended at approximately 1000 hours on day 8. On dosing days, days 1 to 7 of each period (ie, dosing interval; Figure 1), the doses were administered according to the regimen assigned for the period. For regimen A, four 20-mg tablets of febuxostat were administered at 0800 hours with 240 mL of water. For regimen B, four 20-mg tablets of febuxostat and a single 500-mg capsule of naproxen were administered at 0800 hours with 240 mL of water. In addition, a single 500-mg capsule of naproxen was administered at 2000 hours with 240 mL of water. For regimen C, a single 500-mg capsule of naproxen was administered at 0800 hours and at 2000 hours with 240 mL of water. There were 7 days between the last dose in a period and the first dose in the subsequent period when no doses were administered (ie, washout interval; Figure 1). Subjects were not confined on these days. On days 1, 3, 6, and 7 of each period, venous blood samples were collected within 5 minutes before the morning administration of study drugs for the determination of febuxostat and/or naproxen concentrations in plasma. On day 7 of the periods in which febuxostat was administered, venous blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, and

24 hours after the morning administration of study drugs for the determination of febuxostat in plasma. On day 7 of the periods in which naproxen was administered, venous blood samples were collected at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 12.25, 12.5, 13, 13.5, 14, 15, 16, 18, and 24 hours after the morning administration of study drugs for the determination of naproxen concentrations in plasma. On day 8 of period 3, final study procedures were conducted after the 24-hour sample was obtained. Blood samples also were obtained for clinical laboratory testing (eg, hematology/serum chemistry) at screening and days –1, 4, and 8 of each period for subjects who completed the study.

In both studies, the blood specimen was placed on ice immediately after collection. The sealed specimen was kept on ice until centrifuged at approximately 5°C within 2 hours of collection. The plasma was then separated and transferred to a polypropylene vial. All samples were frozen at approximately –20°C until shipped on dry ice to the bioanalytical lab, where they were stored at approximately –20°C until analyzed.

Analytical Methods

Plasma concentrations of febuxostat were measured using a validated method of high-performance liquid chromatography (HPLC) with fluorescence detection at excitation and emission wavelengths of 320 and 380 nm, respectively. In brief, after addition of internal standard (2-naphthoic acid), plasma samples (0.5 mL) were deproteinized by addition of 0.5 mL of acetonitrile, mixed, and centrifuged, and the resulting supernatant was acidified with 50 µL of glacial acetic acid. Febuxostat and the internal standard were resolved from the matrix components using a Phenomenex (Torrance, Calif) Capcell Pak C_{18} column with a mobile phase composed of 0.032% glacial acetic acid in water/acetonitrile (55:45, v:v). The calibration curve range for febuxostat was linear from 0.01 to 20 µg/mL ($R^2 > 0.996$). Quality control (QC) samples (at 0.03, 1, and 15 µg/mL) were analyzed with the plasma samples from each study. The lower limit of quantitation with a 0.5-mL plasma sample was 0.01 µg/mL for febuxostat. In study 1, QC samples showed absolute deviations from the theoretical concentrations of 22.0% or less and coefficients of variation of 106.6% or less for febuxostat. There was 1 anomalous value for the 0.03-µg/mL QC on 1 of the calibration curves, which caused the coefficient of variation to be 106.6% for that QC level. However, the calibration curve met the standard and QC acceptance criteria and was included in the data set. In study 2, QC samples showed absolute deviations from the theoretical concentrations of 7.0% or less and coefficients of variation of 10.3% or less for febuxostat.

Plasma concentrations of indomethacin were determined using a validated HPLC method with UV detection at a wavelength of 260 nm. Briefly, after addition of the internal standard (diclofenac), plasma samples were mixed with the extraction solvent (pentane/methylene chloride; 2:1, v:v), centrifuged, and flash frozen, and the resulting organic phase was evaporated to dryness and reconstituted with the mobile phase (sodium acetate buffer/methanol/acetonitrile;67:13:20, v:v:v). Indomethacin and the internal standard were resolved on a CSC (Montreal, Canada) analytical column (CSC-S ODS-1, 5 µm, 15 cm × 0.46 mm). The calibration curve range for indomethacin was linear from 24.9 to 19920.0 ng/mL ($R^2 > 0.997$). The lower limit of quantitation with a 0.5-mL plasma sample was 24.9 ng/mL for indomethacin. The QC samples (at 75, 7960, and 15 920 ng/mL) analyzed with the plasma samples from this study showed absolute deviations from the theoretical concentrations of 9.4% or less and coefficients of variation of 5.4% or less for indomethacin.

Plasma concentrations of naproxen were determined using a validated HPLC method with fluorescence detection with excitation and emission wavelengths of 230 and 370 nm, respectively. In brief, after addition of the internal standard (2-napthylacetic acid), plasma samples were mixed with the extraction solvent (methylene chloride), centrifuged, and flash frozen, and the resulting organic phase was evaporated and reconstituted with the mobile phase (acetonitrile and phosphoric acid). A Waters (Milford, Mass) symmetry C18 column was used to separate the peaks. The calibration curve for naproxen was linear from 0.1 to 100 µg/mL ($R^2 > 0.993$). The lower limit of quantitation with a 0.1-mL plasma sample was 0.1 µg/mL for naproxen. The QC samples (at 0.25, 3, and 70 µg/mL) analyzed with the plasma samples from this study showed absolute deviations from the theoretical concentrations of 3.3% or less and coefficients of variation of 12.1% or less for naproxen.

Data Analysis

Pharmacokinetic parameters for febuxostat, naproxen, or indomethacin in plasma were determined with standard noncompartmental methods using WinNonlin Professional V.3.1 software (Pharsight Corp, Mountain View, Calif). The pharmacokinetic parameters estimated

Table I Demographic Data for Subjects Completing Studies 1 and 2

Study	Sex,[a] M/F	Age,[b] Y	Race,[c] H/W	Height,[b] cm	Weight,[b] km	Body Mass Index,[b] kg/m²
1 (n = 26)	13/13	36.3 ± 8.7 (21-52)	22/4	166 ± 10 (150-185)	72.7 ± 8.8 (58-95)	26.4 ± 2.2 (22.5-29.7)
2 (n = 24)	11/13	38.0 ± 9.4 (21-53)	21/3	166 ± 9 (150-183)	71.1 ± 10.4 (49-90)	25.7 ± 2.9 (19.5-28.9)

a. Number of male/female subjects completing studies 1 and 2.
b. Data presented are mean ± SD (range).
c. Number of Hispanic/white subjects.

included the observed maximum plasma concentration (C_{max}); t_{max}; the apparent terminal elimination half-life ($t_{1/2}$); the area under the plasma concentration-time curve (AUC) from time 0 to 12 hours after dose (AUC_{12}) for indomethacin or naproxen and from time 0 to 24 hours after dose (AUC_{24}) for febuxostat, indomethacin, or naproxen; the oral clearance (CL/F); and the steady-state apparent volume of distribution (V_{ss}/F).

To assess the effect of indomethacin (study 1) and naproxen (study 2) on the pharmacokinetics of febuxostat, data from the 2 regimens with febuxostat (ie, regimens A and B) were used. Analyses of variance were performed on t_{max} and the natural logarithms of C_{max} and AUC_{24} of febuxostat, with factors for sequence, subjects nested within sequence, period, and regimen. The factor of subjects within sequence was considered random, and all other factors were fixed. The effect of indomethacin and naproxen on the pharmacokinetics of febuxostat was assessed via point estimates and 90% confidence intervals for the ratio of central values of regimen B to regimen A for febuxostat C_{max} and AUC_{24}. In addition, to assess the effect of febuxostat on the pharmacokinetics of indomethacin and naproxen, data from the 2 regimens with indomethacin and naproxen were used (ie, regimens B and C). Analyses of variance were performed on AM t_{max} and the natural logarithms of AM C_{max}, AM AUC_{12}, and AUC_{24} of indomethacin and naproxen, with factors for sequence, subjects nested within sequence, period, and regimen. The factor of subjects within sequence was considered random, and all other factors were fixed. The effect of febuxostat on the pharmacokinetics of indomethacin and naproxen was assessed via point estimates and 90% confidence intervals for the ratio of central values of regimen B to regimen C for AM C_{max}, AM AUC_{12}, and AUC_{24} of indomethacin and naproxen. A conclusion of *no effect* was made if the 90% confidence intervals for the ratios of central values were within the 0.80 to 1.25 range.

RESULTS

Study Subjects

In study 1, 26 (13 male, 13 female) of the 27 subjects enrolled completed the study; 1 subject prematurely discontinued from the study because of an adverse event (contact dermatitis). In study 2, 24 (11 male, 13 female) of the 27 subjects enrolled completed the study; 3 subjects prematurely discontinued from the study because of adverse events (angioedema, abnormal liver function test results, or increased cough). In study 2, 25 of the 27 subjects enrolled completed regimens A and B, whereas 24 of the 27 subjects enrolled completed regimens B and C. A summary of the demographic data for subjects who completed studies 1 and 2 is presented in Table I.

Pharmacokinetics

Effect of Indomethacin on Pharmacokinetics of Febuxostat

In study 1, pharmacokinetic parameters for febuxostat when administered alone (reference) or with indomethacin (test) are presented in Table II. The plasma concentration profile of febuxostat when administered alone and when administered with indomethacin is depicted in Figure 2. The plasma profiles for both regimens overlapped each other, and the mean pharmacokinetic parameters of the 2 regimens were similar. After administration of febuxostat with indomethacin, the median febuxostat t_{max} value remained unchanged, and the mean estimates for other pharmacokinetic parameters, including febuxostat C_{max}, AUC_{24}, $t_{1/2}$, CL/F, and V_{ss}/F, were within 11% of the respective parameters in the febuxostat-alone regimen (Table II). The effects of period and sequence were not statistically significant ($P > .05$) for any of the febuxostat pharmacokinetic parameters

Table II Febuxostat Mean ± SD Pharmacokinetic Parameter Estimates and Geometric Mean Ratios After Multiple Oral Doses of Febuxostat Alone or With Indomethacin or Naproxen

Regimen	t_{max},[a] h	C_{max}, µg/mL	AUC_{24}, µg·h/mL	$t_{1/2}$,[b] h	CL/F, L/h	V_{ss}/F, L
Study 1 (n = 26)						
FBX	1.5 (0.5-3.0)	2.00 ± 0.94	7.13 ± 1.97	6.0 ± 2.5 [5.2]	12.1 ± 3.5	60.2 ± 16.1
FBX + INM	1.5 (0.5-3.0)	1.78 ± 0.49	7.20 ± 1.81	6.0 ± 2.1 [5.2]	11.8 ± 2.8	60.0 ± 15.7
GMR (90% CI)[c]	NA	0.93 (0.82-1.06)	1.02 (0.97-1.06)	NA	NA	NA
Study 2 (n = 25)						
FBX	1.5 (0.5-4.0)	1.75 ± 0.38	6.88 ± 1.56	6.2 ± 1.8 [5.6]	12.3 ± 3.4	58.6 ± 15.0
FBX + NPX	1.5 (0.5-4.0)	2.25 ± 0.56	9.69 ± 2.63	7.8 ± 4.1 [6.7]	8.9 ± 2.7	49.3 ± 14.1
GMR (90% CI)[d]	NA	1.28 (1.18-1.39)	1.40 (1.33-1.46)	NA	NA	NA

AUC_{24}, area under the plasma concentration-time curve from time 0 to 24 hours after dose; CI, confidence interval; CL/F, oral clearance; C_{max}, observed maximum plasma concentration; FBX, febuxostat; GMR, geometric mean ratio; INM, indomethacin; NA, not applicable; NPX, naproxen; $t_{1/2}$, apparent terminal elimination half-life; t_{max}, time to reach the observed maximum plasma concentration; V_{ss}/F, steady-state apparent volume of distribution.
a. Median (range).
b. Harmonic mean in brackets.
c. FBX + INM over FBX geometric mean ratio (the 90% CI of the ratio).
d. FBX + NPX over FBX geometric mean ratio (the 90% CI of the ratio).

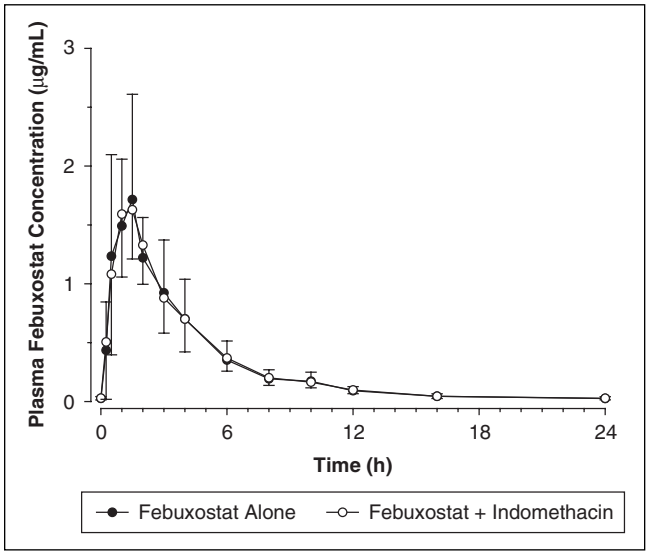

Figure 2. Mean plasma concentration-time profiles of febuxostat after multiple oral doses of febuxostat (80 mg once daily for 5 days) alone or febuxostat and indomethacin (50 mg twice daily for 5 days) in healthy subjects (study 1). Error bars indicate SD.

analyzed. In addition, the 90% confidence intervals for febuxostat C_{max} and AUC_{24} geometric mean ratios for the 2 regimens were within 0.80 to 1.25 (Table II), indicating that indomethacin had no effect on the pharmacokinetics of febuxostat. No statistically significant ($P > .05$) differences were observed between the means of the 2 regimens for febuxostat t_{max} and the natural logarithm of C_{max} and AUC_{24}.

Effect of Febuxostat on Pharmacokinetics of Indomethacin

In study 1, pharmacokinetic parameters for indomethacin when administered alone (reference) or with febuxostat (test) are presented in Table III. The plasma concentration profiles of indomethacin when administered alone and when administered with febuxostat are shown in Figure 3. The plasma profiles for both regimens overlapped each other, and the mean pharmacokinetic parameters of the 2 regimens were similar. After administration of indomethacin with febuxostat, the median indomethacin t_{max} remained relatively unchanged, and the mean estimates for other pharmacokinetic parameters, including indomethacin C_{max}, AUC_{12}, AUC_{24}, $t_{1/2}$ (ie, harmonic), and CL/F, were within 17% of the respective parameters in the indomethacin-alone regimen for both AM and PM doses; the apparent changes in the mean V_{ss}/F estimates did not follow a consistent trend after AM and PM dosing (ie, 24% lower after AM dosing vs 45% higher after PM dosing). These apparent changes were not considered clinically significant because of the high variability associated with some of the mean estimates. The changes in median V_{ss}/F values after administration of indomethacin with febuxostat were within 12% of the median values after administration of indomethacin alone. The effects of period and sequence were not statistically significant ($P > .05$) for any of the pharmacokinetic parameters analyzed, with the exception of the effects of period and sequence on AM AUC_{12}, which were statistically significant ($P \leq .05$), most likely because

Table III Indomethacin Mean ± SD Pharmacokinetic Parameter Estimates and Geometric Mean Ratios After Multiple Oral Doses of Indomethacin Alone or With Febuxostat in Study 1

Regimen (n = 26)	t_{max},[a] h	C_{max}, µg/mL	AUC_{12}, µg·h/mL	AUC_{24}, µg·h/mL	$t_{1/2}$,[b] h	CL/F, L/h	V_{ss}/F, L
AM dose							
INM	1.3 (0.5-3.0)	2.76 ± 0.54	8.71 ± 2.06	17.80 ± 3.80	7.2 ± 4.1 [5.2]	3.02 ± 0.67	22.5 ± 9.0
FBX + INM	1.5 (1.0-4.0)	2.74 ± 0.68	9.26 ± 1.80	17.69 ± 3.36	5.7 ± 1.7 [5.2]	2.79 ± 0.51	17.2 ± 4.7
GMR (90% CI)[c]	NA	0.98 (0.91-1.06)	1.07 (1.04-1.10)	1.00 (0.96-1.03)	NA	NA	NA
PM dose							
INM	2.0 (1.0-6.0)	1.92 ± 0.65	9.09 ± 1.96	17.80 ± 3.80	4.9 ± 2.4 [4.2]	2.87 ± 0.60	22.1 ± 7.0
FBX + INM	2.0 (0.5-6.0)	1.77 ± 0.63	8.43 ± 1.91	17.69 ± 3.36	5.7 ± 3.4 [4.4]	3.37 ± 2.21	32.1 ± 40.2

AUC_{12}, area under the plasma concentration-time curve from time 0 to 12 hours after dose; AUC_{24}, area under the plasma concentration-time curve from time 0 to 24 hours after dose; CI, confidence interval; CL/F, oral clearance; C_{max}, observed maximum plasma concentration; FBX, febuxostat; GMR, geometric mean ratio; INM, indomethacin; NA, not applicable; $t_{1/2}$, apparent terminal elimination half-life; t_{max}, time to reach the observed maximum plasma concentration; V_{ss}/F, steady-state apparent volume of distribution.

a. Median (range).

b. Harmonic mean in brackets.

c. FBX + INM over INM geometric mean ratio (the 90% CI of the ratio).

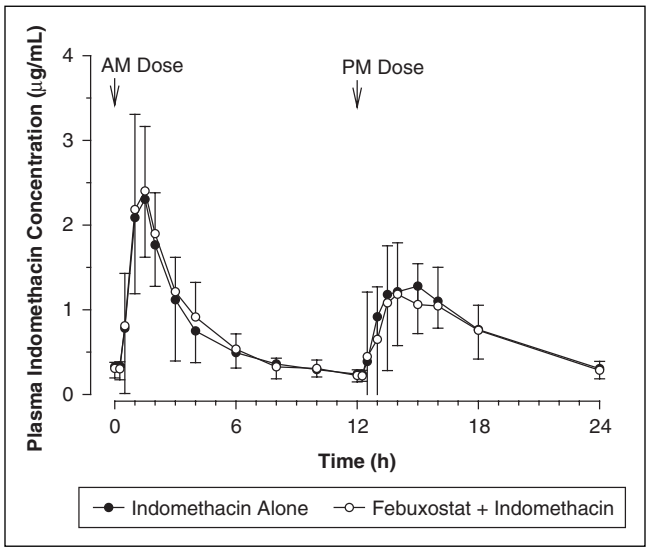

Figure 3. Mean plasma concentration-time profiles of indomethacin after multiple oral doses of indomethacin (50 mg twice daily for 5 days) alone or febuxostat (80 mg once daily for 5 days) and indomethacin in healthy subjects (study 1). Error bars indicate SD.

of random assignment of subjects to sequence groups. In addition, the 90% confidence intervals for AM C_{max}, AM AUC_{12}, and AUC_{24} geometric mean ratios of the 2 regimens were within 0.80 to 1.25 (Table III), indicating that febuxostat had no effect on the pharmacokinetics of indomethacin. No statistically significant ($P > .05$) differences between the means of the 2 regimens were observed for AM indomethacin t_{max} and the natural logarithm of C_{max}, AUC_{12}, and AUC_{24}.

Effect of Naproxen on Pharmacokinetics of Febuxostat

In study 2, pharmacokinetic parameters for febuxostat when administered alone (reference) or with naproxen (test) are presented in Table II. The plasma concentration profile of febuxostat when administered alone and when administered with naproxen is illustrated in Figure 4. In addition, the mean and individual plots of febuxostat C_{max} and AUC_{24} for febuxostat alone and febuxostat-with-naproxen regimens are presented in Figure 5. The plasma febuxostat concentration profile for febuxostat when administered with naproxen appeared to be higher as compared to when administered alone. After administration of febuxostat with naproxen, febuxostat mean t_{max} remained relatively unchanged, but febuxostat mean C_{max}, AUC_{24}, and $t_{1/2}$ increased by approximately 28%, 41%, and 26%, respectively, as compared to the mean values after administration of febuxostat alone. In addition, the febuxostat mean CL/F and V_{ss}/F values decreased by 28% and 16%, respectively, after administration of febuxostat with naproxen. The effects of period and sequence were not statistically significant ($P > .05$) for any of the febuxostat pharmacokinetic parameters analyzed. The 90% confidence intervals of febuxostat C_{max} and AUC_{24} geometric mean ratios for the 2 regimens extended above the upper bound of the 0.80 to 1.25 no-effect range (Table II). Febuxostat C_{max} and AUC_{24} geometric means were higher by approximately 28% and 40%, respectively, for the febuxostat-with-naproxen regimen as compared to the febuxostat-alone regimen. In addition, the differences between

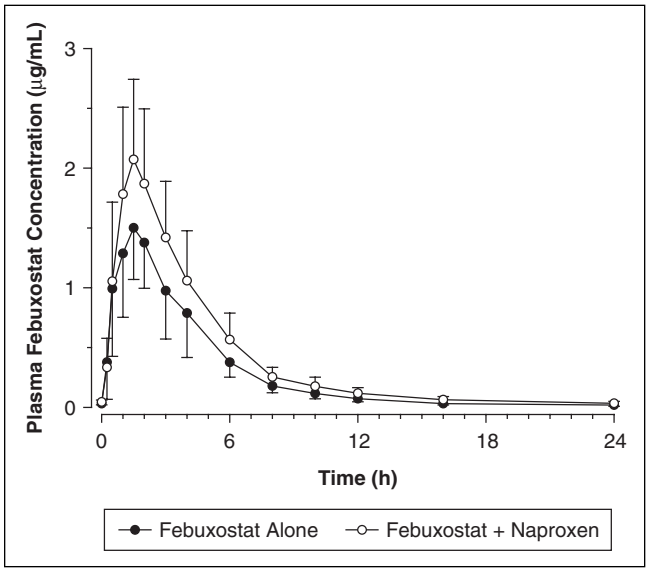

Figure 4. Mean plasma concentration-time profiles of febuxostat after multiple oral doses of febuxostat (80 mg once daily for 7 days) alone or febuxostat and naproxen (500 mg twice daily for 7 days) in healthy subjects (study 2). Error bars indicate SD.

the means of the natural logarithms of febuxostat C_{max} and AUC_{24} for the 2 regimens were statistically significant ($P \leq .05$).

Effect of Febuxostat on Pharmacokinetics of Naproxen

In study 2, pharmacokinetic parameters for naproxen when administered alone (reference) or with febuxostat (test) are presented in Table IV. The plasma concentration profiles of naproxen when administered alone and when administered with febuxostat are presented in Figure 6. The mean plasma profiles for both regimens overlapped each other, and the mean pharmacokinetic parameters between the 2 regimens were similar. After administration of naproxen with febuxostat, the median t_{max} of naproxen remained unchanged for the AM dose and was delayed by 0.5 hours for the PM dose as compared to the naproxen-alone regimen. The naproxen mean C_{max}, AUC_{12}, AUC_{24}, $t_{1/2}$ (ie, harmonic), CL/F, and V_{ss}/F values for the naproxen-with-febuxostat regimen were within 12% of the respective parameters in the naproxen-alone regimen for both the AM and PM doses. The effects of period and sequence were not statistically significant ($P > .05$) for any of the naproxen pharmacokinetic parameters analyzed. In addition, the 90% confidence intervals for C_{max} and AUC geometric mean ratios of the 2 regimens were within 0.80 to 1.25, indicating that febuxostat had no effect on the pharmacokinetics of naproxen. No statistically significant ($P > .05$) differences between the means of the 2 regimens were observed for AM naproxen t_{max} and the natural logarithm of C_{max}, AUC_{12}, and for AUC_{24}.

Safety

In study 1, the overall incidence of treatment-related adverse events was 8% in the febuxostat-alone regimen, 22% in the febuxostat-plus-indomethacin regimen, and 27% in the indomethacin-alone regimen. The only treatment-related adverse events reported

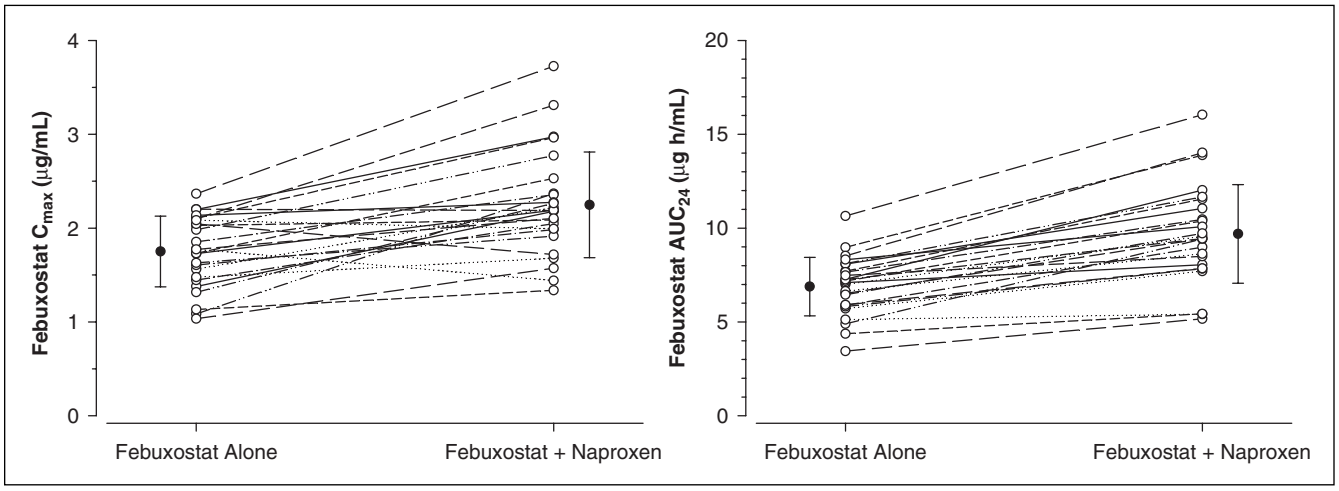

Figure 5. Mean (solid circle) and individual (empty circle) plots for febuxostat maximum plasma concentration (C_{max}) (A) and area under the plasma concentration-time curve from time 0 to 24 hours after dose (AUC_{24}) (B) after multiple oral doses of febuxostat (80 mg once daily for 7 days) alone or febuxostat and naproxen (500 mg twice daily for 7 days) in healthy subjects (study 2). Error bars indicate SD.

Table IV Naproxen Mean ± SD Pharmacokinetic Parameter Estimates and Geometric Mean Ratios After Multiple Oral Doses of Naproxen Alone or With Febuxostat in Study 2

Regimen (n = 24)	t_{max},[a] h	C_{max}, µg/mL	AUC_{12}, µg·h/mL	AUC_{24}, µg·h/mL	$t_{1/2}$,[b] h	CL/F, L/h	V_{ss}/F, L
AM dose							
NPX	1.5 (1.0-4.0)	93.7 ± 7.1	792 ± 66	1569 ± 128	11.3 ± 3.8 [10.4]	0.64 ± 0.05	10.4 ± 2.5
FBX + NPX	1.5 (1.0-4.0)	93.8 ± 6.3	802 ± 67	1562 ± 118	10.2 ± 3.1 [9.2]	0.63 ± 0.05	9.3 ± 2.2
GMR (90% CI)[c]	NA	1.00 (0.98-1.03)	1.01 (0.99-1.03)	1.00 (0.98-1.01)	NA	NA	NA
PM dose							
NPX	2.5 (1.5-6.0)	86.9 ± 8.9	778 ± 71	1569 ± 128	13.6 ± 2.9 [13.1]	0.65 ± 0.07	13.9 ± 3.3
FBX + NPX	3.0 (1.0-6.0)	83.6 ± 10.3	761 ± 58	1562 ± 118	13.5 ± 4.1 [12.5]	0.66 ± 0.05	14.5 ± 4.8

AUC_{12}, area under the plasma concentration-time curve from time 0 to 12 hours after dose; AUC_{24}, area under the plasma concentration-time curve from time 0 to 24 hours after dose; CI, confidence interval; CL/F, oral clearance; C_{max}, observed maximum plasma concentration; FBX, febuxostat; GMR, geometric mean ratio; NA, not applicable; NPX, naproxen; $t_{1/2}$, apparent terminal elimination half-life; t_{max}, time to reach the observed maximum plasma concentration; V_{ss}/F, steady-state apparent volume of distribution.

a. Median (range).

b. Harmonic mean in brackets.

c. FBX + NPX over NPX geometric mean ratio (the 90% CI of the ratio).

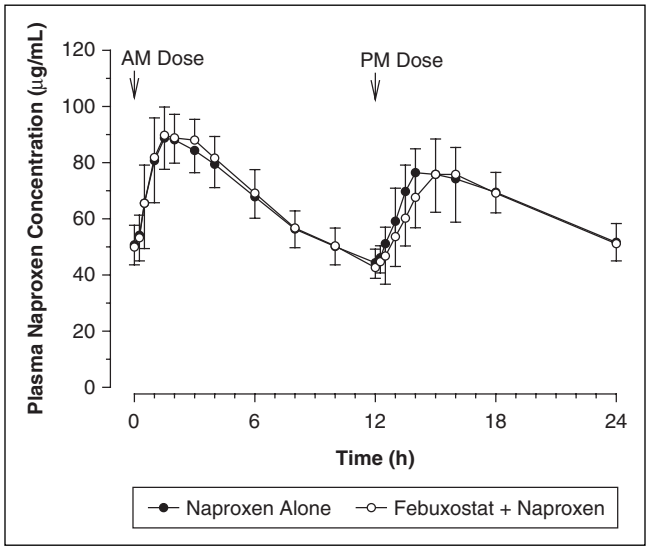

Figure 6. Mean plasma concentration-time profiles of naproxen after multiple oral doses of naproxen (500 mg twice daily for 7 days) alone or febuxostat (80 mg] once daily for 7 days) and naproxen in healthy subjects (study 2). Error bars indicate SD.

by 2 or more subjects in any regimen were headache and dyspepsia (Table V). After 5 days of dosing with febuxostat and indomethacin, 1 subject discontinued from the study because of an adverse event (contact dermatitis), which the investigator considered unlikely related to the study drug.

In study 2, the overall incidence of treatment-related adverse events was 28% in the febuxostat-alone regimen, 35% in the febuxostat-plus-naproxen regimen, and 26% in the naproxen-alone regimen. The only adverse events reported by 2 or more subjects in any regimen were constipation, diarrhea, dyspepsia, nausea, and dizziness (Table VI). Three subjects discontinued from the study because of adverse events (ie, angioedema, abnormal liver function test results, and increased cough). The investigator considered the abnormal liver function test results probably related to naproxen. The investigator considered the angioedema possibly related to naproxen (occurred only during naproxen dosing), with an alternate cause of NSAID allergy, and the increased cough (occurred only during naproxen dosing) was considered unlikely related to study drug, with an alternate cause of asthma.

In both studies, results of other safety analyses demonstrated no clinically significant changes in results of clinical laboratory evaluations, physical examinations, vital signs measured, or electrocardiographic testing. There were no deaths or serious adverse events. All adverse events were mild or moderate and self-limiting.

DISCUSSION

Febuxostat had no effect on the pharmacokinetics of indomethacin and naproxen. Both indomethacin and naproxen are metabolized extensively and undergo glucuronide conjugation and oxidation.[20,30] Approximately 50% of the naproxen oral dose is recovered in urine as the acyl-glucuronide of naproxen.[20,24] In regard to indomethacin, a small percentage of the oral dose (ie, approximately 13%) was recovered in urine as the glucuronide conjugate of indomethacin.[23,30] However, large amounts of the glucuronide conjugate of indomethacin were recovered in the bile undergoing

Table V Summary of Frequent Treatment-Related Adverse Events During Treatment After Multiple Oral Doses of Febuxostat or Indomethacin Alone or Combined in Study 1

Adverse Event	FBX (n = 26)	FBX + INM (n = 27)	INM (n > 26)
Subject with at least 1 adverse event	2 (8)	6 (22)	7 (27)
Headache	0 (0)	4 (15)	4 (15)
Dyspepsia	0 (0)	2 (7)	1 (4)

Adverse events reported by at least 2 subjects in any regimen. FBX, febuxostat; INM, indomethacin.

Table VI Summary of Frequent Treatment-Related Adverse Events During Treatment After Multiple Oral Doses of Febuxostat or Naproxen Alone or Combined in Study 2

	FBX (n = 25)		FBX + NPX (n = 26)		NPX (n = 27)	
Adverse Event	n	(%)	n	(%)	n	(%)
Subject with at least 1 adverse event	7	(28)	9	(35)	7	(26)
Constipation	1	(4)	3	(12)	4	(15)
Diarrhea	2	(8)	0	(0)	2	(7)
Dyspepsia	0	(0)	2	(8)	1	(4)
Nausea	2	(8)	1	(4)	0	(0)
Dizziness	3	(12)	1	(4)	0	(0)

Adverse events reported by at least 2 subjects in any regimen. FBX, febuxostat; NPX, naproxen.

subsequent enterohepatic recycling.[31,32] Therefore, the 13% renal recovery of the glucuronide conjugate of indomethacin may lead to underestimating the importance of the glucuronidation pathway in eliminating indomethacin from the body. Any change in the renal or biliary excretion of conjugated indomethacin can have an effect on the extent of enterohepatic recycling and subsequently the total exposure to the drug. In both studies, no urinary or biliary excretion data were collected for indomethacin, naproxen, or febuxostat. However, the lack of effect on the plasma pharmacokinetics of indomethacin and naproxen by febuxostat may indicate that febuxostat or its metabolites did not affect the glucuronidation of indomethacin and naproxen, renal/biliary excretion of the glucuronide conjugates of indomethacin and naproxen, or other oxidative metabolic pathways involved in the elimination of indomethacin and naproxen. Probenecid, a uricosuric antihyperuricemic agent, caused an increase in the total exposure to both naproxen and indomethacin by potentially inhibiting the glucuronidation pathway and/or decreasing the renal clearance of their glucuronide conjugates.[25,26]

After administration of febuxostat with indomethacin, indomethacin had no effect on the pharmacokinetics of febuxostat. However, administration of febuxostat with naproxen caused an increase in plasma exposure to febuxostat. The 90% confidence intervals for febuxostat C_{max} and AUC_{24} geometric mean ratios of the 2 regimens extended above the 0.80 to 1.25 no-effect range after administration of febuxostat with naproxen as compared to febuxostat alone at steady state. Febuxostat C_{max} and AUC_{24} central values were higher by approximately 28% and 40%, respectively, for the febuxostat-with-naproxen regimen as compared to the febuxostat-alone regimen. Naproxen at the doses administered likely may have inhibited the glucuronidation pathway of febuxostat.[27,28] In addition, similar to febuxostat and its metabolites, naproxen and its conjugated metabolite also undergo renal elimination. Therefore, it also is possible that naproxen decreased renal clearance of the glucuronidated febuxostat and subsequently increased the extent of its biliary excretion, ultimately increasing the extent of enterohepatic recycling of febuxostat. A possible inhibition of febuxostat glucuronidation by naproxen would cause an increase in both febuxostat C_{max} and AUC_{24}, whereas a decrease in renal clearance of conjugated febuxostat and consequently an increase in the extent of enterohepatic recycling of febuxostat would

have caused an increase only in AUC_{24} of febuxostat. Therefore, even though no urinary excretion data were collected for conjugated febuxostat during this study, on the basis of this study's plasma pharmacokinetic results, it is very likely that the increase in the C_{max} and AUC_{24} of febuxostat was mainly the result of the inhibitory effect of naproxen on the glucuronidation of febuxostat. In fact, naproxen is known to compete for some of the same UGT isozymes involved in the metabolism of febuxostat (ie, UGT 1A1, 1A9, and 2B7).[28,33]

Although coadministration of naproxen 500 mg twice daily with febuxostat 80 mg once daily can cause a 40% increase in febuxostat plasma total exposure, the mean AUC_{24} for febuxostat after administration of an 80-mg dose of febuxostat with naproxen is much lower than the mean steady-state AUC_{24} value with 300 mg of febuxostat (9.69 µg·h/mL vs 48.36 µg·h/mL [unpublished data]). Because multiple 300-mg oral doses of febuxostat have been used safely in healthy subjects for 7 days, the increase in AUC_{24} of febuxostat when administered with naproxen 500 mg twice daily is not expected to cause any safety concerns. In addition, febuxostat doses of 240 mg once daily for as long as 28 weeks have been used in gout patients with no safety concerns.[34] The proposed doses of febuxostat for the management of hyperuricemia in gout patients are 80 mg and 120 mg of febuxostat once daily.[15]

Although assessment of the chronokinetics of indomethacin and naproxen[35] was not part of the study objectives, the pharmacokinetic data obtained from AM and PM dosing of indomethacin and naproxen provided additional information about the effect of the time of dosing on the pharmacokinetics of indomethacin and naproxen. The chronokinetic data for both indomethacin and naproxen indicate that even though PM dosing compared to AM dosing caused a delay in t_{max} and a slight decrease in C_{max} mean values, AUC_{12} mean values were not affected and remained relatively unchanged for both indomethacin and naproxen. The delay in t_{max} and decrease in C_{max} mean values most likely were caused by a decrease in the absorption rate constant due to PM versus AM differences in the gastrointestinal physiological parameters (eg, gastric pH and gastrointestinal motility). Because AUC_{12} was not affected by PM versus AM dosing, this lack of change indicates that the decrease in the absorption rate constant with PM dosing as compared to AM dosing was not associated with a decrease in bioavailability and elimination of indomethacin and naproxen.

After administration of febuxostat with either indomethacin or naproxen, the incidence of treatment-related adverse events was not clinically significantly different than that observed with the administration of indomethacin or naproxen alone, respectively (22% vs 27% and 35% vs 26%, respectively; Tables V and VI). In general, a high incidence of headache and consti pation was associated with the use of indomethacin and naproxen, respectively. Overall, however, all adverse events were mild to moderate and self-limiting, and coadministration of febuxostat with either indomethacin or naproxen did not raise any clinically significant safety concerns.

In conclusion, febuxostat had no effect on the plasma pharmacokinetics of indomethacin and naproxen. Similarly, indomethacin had no effect on the plasma pharmacokinetics of febuxostat. Although naproxen caused an increase in plasma exposure to febuxostat, this increase is not expected to be clinically significant. Therefore, based on the plasma pharmacokinetic data in healthy subjects, febuxostat may be administered with indomethacin or naproxen with no dose adjustments for febuxostat, indomethacin, or naproxen.

The authors would like to thank Stuart I. Harris, MD, PhD, for performing the clinical studies; Galen Witt, MS, for statistical assistance; Patricia MacDonald, RN, NP, and Christopher Lademacher, MD, for review of the manuscript; Paula Bargiel, MA, for editorial support; and MDS Pharma Services (Lincoln, Neb and St. Laurent, Quebec) and PPD Development (Richmond, Va) for performing the bioanalytical sample analyses. All authors are employees of TAP Pharmaceutical Products, Inc.

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