CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA:	21-042/S-008
SUBMISSION DATE:	07/10/00
TYPE OF SUBMISSION:	Labeling Supplement
PRODUCT:	Vioxx (rofecoxib) Tablets, 12.5 mg & 25 mg
SPONSOR:	Merck
REVIEWERS:	Jang-Ik Lee, Pharm.D., Ph.D. and Sue-Chih Lee, Ph.D.
TEAM LEADER:	Dennis Bashaw, Pharm.D.
OCPB DIVISION:	DPE III, HFD-880
ORM DIVISION:	ODE V, HFD-550

I. EXECUTIVE SUMMARY

Vioxx is an orally active cyclooxygenase-2 inhibitor and was approved by the Agency on May 20, 1999 for the management of acute pain and OA. This supplemental application included three pharmacokinetics studies (one hepatic impairment study and two drug-drug interaction studies with methotrexate and theophylline) to provide for changes to the package insert and patient product information.

Drug-drug interactions: Rofecoxib-methotrexate interaction study (Reference 101) showed that rofecoxib 12.5, 25, and 50 mg once daily has no effect on the plasma concentrations or renal clearance of methotrexate in RA patients. In contrast, rofecoxib-theophylline interaction study (Reference 114) showed that rofecoxib 12.5, 25, and 50 mg once daily moderately increases the theophylline plasma concentrations (increase in single-dose $AUC_{0-\infty}$ by 38 to 60% without change in Cmax) in association with a prolonged elimination half-life. Thus, theophylline plasma concentrations should be monitored when rofecoxib treatment is initiated or changed.

PK in moderate hepatic impairment patients: At steady state conditions following multiple dosing of rofecoxib tablets 12.5 mg daily, patients with moderate hepatic impairment had a higher Cmax (↑53%) and AUC (↑55%). Because of the concern about cardiovascular adverse events with rofecoxib, we recommend that moderate hepatic impairment patients should start with the lowest possible dose with careful monitoring of signs and symptoms of adverse events.

II. LABELING COMMENTS

The sponsor's revised label is acceptable except for the following:

1. "CLINICAL PHARMACOLOGY" section, under "Special Populations"

Hepatic Insufficiency

A single-dose pharmacokinetic study in mild (Child-Pugh score≤6) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. A pharmacokinetic study in patients with moderate (Child-Pugh score 7-9) hepatic insufficiency indicated that rofecoxib plasma concentrations were higher (mean AUC: ~ 55%; mean Cmax:

53%) relative to healthy subjects. Patients with severe hepatic insufficiency have not been studied.

2. "PRECAUTIONS" section, under "Drug Interactions"

Methotrexate: VIOXX 12.5, 25, and 50 mg, each dose administered once daily for 7 days, had no effect on the plasma concentration of methotrexate as measured by AUC_{0-24h} in patients receiving single weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. At higher than recommended doses, VIOXX 75 mg administered once daily for 10 days increased plasma concentrations by 23% as measured by AUC_{0-24hr} in patients receiving methotrexate 7.5 to 15 mg/week for rheumatoid arthritis. At 24 hours postdose, a similar proportion of patients treated with methotrexate alone (94%) and subsequently treated with methotrexate co-administered with 75 mg of rofecoxib (88%) had methotrexate plasma concentrations below the measurable limit (5 ng/mL). Standard monitoring of methotrexate related toxicity should be continued if VIOXX and methotrexate are administered concomitantly.

Theophylline: VIOXX 12.5, 25, and 50 mg administered once daily for 7 days increased plasma theophylline concentrations in healthy subjects administered a single 300 mg dose of theophylline. Adequate monitoring of theophylline plasma concentrations should be considered when therapy with VIOXX is initiated or changed in patients receiving theophylline.

These data suggest that rofecoxib may produce a modest inhibition of cytochrome P450 (CYP) 1A2. Therefore, there is a potential for an interaction with other drugs that are metabolized by CYP 1A2 (e.g., amitriptyline, tacrine, and zileuton).

3. "DOSAGE AND ADMINISTRATION" section

Dosing recommendation for moderate hepatic impairment patients should be added to read as follows:

Hepatic Insufficiency: Because of significant increases in both AUC and Cmax, patients with moderate hepatic impairment (Child-Pugh score: 7-9) should be treated with the lowest possible dose (see CLINICAL PHARMACOLOGY, Special Populations).

III. RECOMMENDATION

All labeling comments listed above should be communicated to the sponsor.

Jang-Ik Lee, Pharm.D., Ph.D. Sue-Chih Lee, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____

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IV. INDIVIDUAL STUDY REVIEW

REFERENCE 101: A DOUBLE-BLIND, PARALLEL STUDY TO INVESTIGATE THE EFFECT OF MK-0966 (ROFECOXIB) (12.5, 25, AND 50 MG) ON ORAL METHOTREXATE PHARMACOKINETICS IN RHEUMATOID ARTHRITIS PATIENTS

BACKGROUND

Oral methotrexate is a commonly used treatment for active rheumatoid arthritis and is frequently used in combination with other anti-inflammatory medications. Rofecoxib can influence the plasma pharmacokinetics of methotrexate possibly through competition for the anionic secretory channel in the kidney with a subsequent reduction in renal clearance. In previous studies, the effect was smaller with rofecoxib 75-mg dose as compared with that at 250 mg, suggesting a dose-related phenomenon. Thus, it is possible that recommended clinical doses of rofecoxib (12.5, 25, and 50 mg daily) may have little or no effect on the pharmacokinetics of methotrexate. This study was conducted to evaluate the effect of clinical doses of rofecoxib on methotrexate.

OBJECTIVES

To determine the effect of three doses (12.5, 25, and 50 mg) of rofecoxib on methotrexate plasma concentration profiles.

STUDY DESIGN

This was a randomized, fixed-sequence, double-blind, placebo-controlled study in 25 RA patients. Patients received oral methotrexate on Days -1, 7, 14, and 21 in the fasting state. The dose of methotrexate was that previously individualized as per the patients' clinical status by the patients' physician, stable over at least the past one month and continued throughout the study. Nineteen patients were to receive rofecoxib 12.5, 25, and 50 mg once daily on Days 1 to 7, 8 to 14, and 15 to 21, respectively. Six patients were to receive placebo on Days 1 to 21. Blood samples were collected at the following time points over 24 hours for methotrexate and 7-hydroxymethotrexate assay: predose, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, and 24 hours postdose. Urine samples were collected predose (-2 to 0 hours), and 0 to 2 hours, 2 to 4 hours, 4 to 6 hours, 6 to 12 hours, and 12 to 24 hours after each methotrexate dose.

Inclusion/Exclusion Criteria: Male and nonpregnant female patients who had been treated with a stable dose of oral methotrexate (7.5 - 20 mg/week) for at least 1 month were included in this study. However, patients who were on NSAIDs were excluded. These and other inclusion/exclusion criteria are appropriate to achieve the study objectives.

METHODS

Study Drugs: Rofecoxib 12.5 and 25 mg tablets (Batch No. MR-3475 and MR-3481, respectively) and corresponding placebo (MR-3551 and MR-3529, respectively) was provided in individual kits for each patient. Rofecoxib 2 x 25-mg tablets were used for 50-mg dosing. Methotrexate sodium tablets (2.5 mg, Batch No. MR-3886) were used.

Diet: On Days -1, 7, 14 and 21, the patient must fast from midnight on the night prior to dosing of methotrexate until 4 hours postdose. There were no dietary restrictions on Days 1 through 6, Days 8 through 13, and Days 15 through 20.

Evaluation Criteria: The effect of three doses of rofecoxib (12.5, 25, and 50 mg) on oral methotrexate pharmacokinetics was evaluated by area under the total methotrexate plasma concentration curve ($AUC_{0-\infty}$), maximum concentration (Cmax), time to reach maximum concentration (Tmax), apparent terminal half-life ($t_{1/2}$), and concentration at 24 hours postdose of total methotrexate in plasma (C_{24}) prior to and after rofecoxib treatment. Similar pharmacokinetic parameters ($AUC_{0\text{-}24\ hr}$, Cmax, and Tmax) were used to evaluate the effect of rofecoxib on oral 7-hydroxymethotrexate pharmacokinetics. Urinary parameters (total urinary recovery and renal clearance of total methotrexate and 7-hydroxymethotrexate) were also examined. Safety was determined by clinical observations and laboratory measurements.

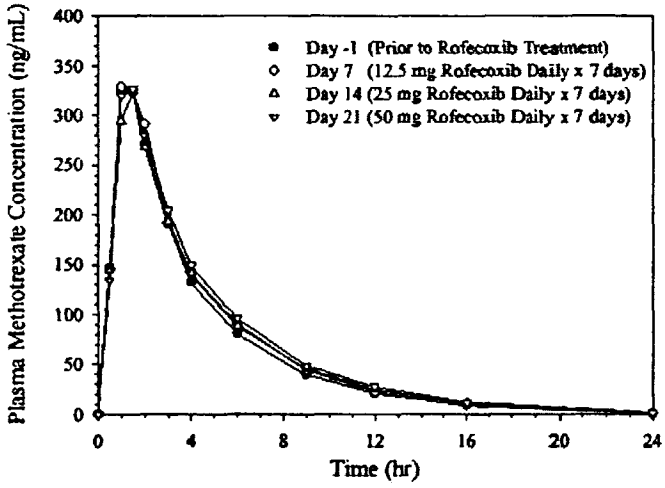
Statistical Analysis: A 90% confidence interval (CI) for the geometric mean ratio (GMR) of rofecoxib (12.5 mg) administration with methotrexate (Day 7) to methotrexate alone (Day -1) was calculated for total methotrexate $AUC_{0-\infty}$. If the CI was contained within [redacted], then it was concluded that the plasma $AUC_{0-\infty}$ of total methotrexate after 7 days of rofecoxib was similar to that observed immediately prior to rofecoxib administration. The above procedure was also used for the Cmax, Tmax, and apparent terminal t½ of total methotrexate. For 7-hydroxymethotrexate, pharmacokinetic parameters ($AUC_{0-24\ hr}$, Cmax, and Tmax) were assessed as described above. Urinary recovery and renal clearance for methotrexate and 7-hydroxymethotrexate were also analyzed. The GMR of the renal clearance of methotrexate was used to confirm the plasma $AUC_{0-\infty}$ GMR results. The number of patients exhibiting total plasma methotrexate concentrations greater than 5.0 ng/mL (limit of quantification) at 24 hours following the administration of methotrexate was evaluated.

RESULTS

A total of 25 RA patients aged between 32 and 75 years old entered in this study. Twenty-one patients completed the study (18 on rofecoxib and 3 on placebo). There were 6 males and 19 females, and 21 whites and 4 blacks.

Pharmacokinetics: The mean plasma concentration profiles of total methotrexate are in the following figure.

Mean Concentrations of Methotrexate in Plasma Following Administration of Methotrexate and Daily Doses of Rofecoxib to Rheumatoid Arthritis Patients (n=18) (Normalized to 12.5-mg Dose of Methotrexate)



The geometric mean $AUC_{0-\infty}$ values of total methotrexate prior to rofecoxib administration and after each dose of rofecoxib (12.5, 25, and 50 mg) are summarized in the table below. The methotrexate $AUC_{0-\infty}$ values for all three doses of rofecoxib were not significantly different from the methotrexate $AUC_{0-\infty}$ values prior to rofecoxib administration ($p > 0.200$). The 90% CI for

the GMR of methotrexate $AUC_{0-\infty}$ (rofecoxib plus methotrexate / methotrexate alone) fell within the prespecified bounds of [redacted] for all three doses.

Summary Statistics for $AUC_{0-\infty}$ (ng·hr/ml) of Total Methotrexate in Patients on Rofecoxib or Placebo (Normalized to 12.5-mg Dose of Methotrexate)

Treatment	Day	N	Geometric LS Mean	Median	Min, Max	Between-Patient Geometric SD[†]	Approximate Within-Patient CV[‡]	GMR[§]	(90% CI for GMR)	p-Value Versus Baseline[¶]
Baseline	-1	18	1515	1528	[redacted]	403	16.58	.	.	.
Rofecoxib (12.5 mg)	7	18	1567	1405		434		1.03	(0.94, 1.14)	0.541
Rofecoxib (25 mg)	14	18	1541	1498		458		1.02	(0.92, 1.12)	0.755
Rofecoxib (50 mg)	21	18	1607	1544		588		1.06	(0.96, 1.17)	0.289

† The between-patient standard deviation (SD) was back-transformed from the log scale using the following formula: geometric least-square means $\cdot\sqrt{e^{s^2}\cdot(e^{s^2}-1)}$ where s^2 = log scale standard deviation.
‡ Approximate within-patient coefficient of variation (CV) is the root mean square error on log scale • 100.
§ GMR represents either Day 7/Day -1, Day 14/Day -1, or Day 21/ Day-1.
¶ Overall treatment p-value was 0.742 for the rofecoxib group.
# Sample size for the placebo patients (n=3) is too small for inferential testing.

Similarly, as shown in the table below, methotrexate Cmax values for all three doses of rofecoxib were not significantly different from the methotrexate Cmax values prior to rofecoxib administration ($p > 0.200$) and the 90% CIs for the GMR of methotrexate Cmax for all three rofecoxib doses fell within the prespecified bounds of [redacted]

Summary Statistics for Cmax (ng/ml) of Total Methotrexate in Patients on Rofecoxib or Placebo (Normalized to 12.5-mg Dose of Methotrexate)

Treatment	Day	N	Geometric LS Mean	Median	Min, Max	Between-Patient Geometric SD[†]	Approximate Within-Patient CV[‡]	GMR[§]	(90% CI for GMR)	p-Value Versus Baseline[¶]
Baseline	-1	18	390	347	[redacted]	126	19.80	.	.	.
Rofecoxib (12.5 mg)	7	18	391	393		134		1.00	(0.89, 1.12)	0.990
Rofecoxib (25 mg)	14	18	362	359		116		0.93	(0.83, 1.04)	0.263
Rofecoxib (50 mg)	21	18	382	399		152		0.98	(0.87, 1.10)	0.736

† The between-patient SD was back-transformed from the log scale using the following formula: geometric least-square means $\cdot\sqrt{e^{s^2}\cdot(e^{s^2}-1)}$ where s^2 = log scale standard deviation.
‡ Approximate within-patient CV is the root mean square error on log scale • 100.
§ GMR represents either Day 7/Day -1, Day 14/Day -1, or Day 21/Day-1.
¶ Overall treatment p-value was 0.633 for the rofecoxib group.
# Sample size for the placebo patients (n=3) is too small for inferential testing.

There was no significant difference in Tmax of total methotrexate after rofecoxib administration (12.5, 25, or 50 mg rofecoxib) versus that prior to rofecoxib administration; the median Tmax ranged from 1.00 to 1.50 hours ($p > 0.200$ versus baseline) across all groups. The harmonic mean apparent terminal t½ of total methotrexate was 3.06, 2.96, 3.18, and 3.15 hours prior to administration of rofecoxib and after rofecoxib 12.5, 25, and 50 mg, respectively. No significant difference from baseline was noted following the 12.5-, 25-, or 50-mg dose of rofecoxib ($p > 0.200$) compared with methotrexate alone. At 24 hours postdose, a similar proportion of patients treated with methotrexate alone (94%), with methotrexate plus rofecoxib 12.5 mg (89%), with methotrexate plus rofecoxib 25 mg (89%), and with methotrexate plus rofecoxib 50 mg (83%) had methotrexate plasma concentrations below 5 ng/mL (limit of quantitation).

The geometric mean renal clearance of methotrexate was 102.0 mL/min at baseline and 93.1 mL/min after 7 days of rofecoxib 50 mg (Day 21). The GMR of the methotrexate renal clearance was 0.91, with a 90% CI of [0.82, 1.02]. Summary statistics of renal clearance of methotrexate are in the following table. The geometric mean urinary recovery of methotrexate after 7 days of dosing with rofecoxib 50 mg (8.9 mg) was not significantly different from that on Day –1 (9.2 mg, p = 0.683). These results are consistent with the lack of effect of rofecoxib on total methotrexate $AUC_{0-\infty}$ at these doses.

Summary Statistics for Renal Clearance of Methotrexate (mL/min)

Treatment	Day	N	Geometric LS Mean	Median	Min, Max	Between-Patient Geometric SD[†]	Approximate Within-Patient CV[‡]	GMR[¶]	(90% CI for GMR)	p-Value Versus Baseline[‖]
Baseline	-1	18	102.0	106.0	——	27.5	19.50	0.91	(0.82, 1.02)	0.178
Rofecoxib (50 mg)	21	18	93.1	102.4	——	45.0				

† The between-patient SD was back-transformed from the log scale using the following formula: geometric least-square means $\cdot\sqrt{e^{s^2}\cdot(e^{s^2}-1)}$ where s^2 =log scale standard deviation.
‡ Approximate within-patient CV is the root mean square error on log scale · 100.
¶ GMR represents Day 21/Day-1.
‖ Sample size for the placebo patients (n=3) is too small for inferential testing.

The results of AUC_{0-24}, Cmax, Tmax, urinary recovery, and renal clearance for 7-hydroxymethotrexate were also consistent with those for total methotrexate (data not shown here). However, the sponsor did not count the contribution of 7-hydroxymethotrexate after 24 hours post methotrexate administration to these results. Plasma trough concentrations of rofecoxib increased in a dose-proportional manner.

Safety: Sixteen patients had a total of 44 clinical adverse experiences, none of which were serious. Three patients discontinued (2 on placebo, 1 on rofecoxib) because of clinical adverse experiences and one due to laboratory measurements outside normal limits, all of which were considered definitely not related to study drug.

CONCLUSIONS

(1) Rofecoxib 12.5, 25, and 50 mg once daily has no effect on the plasma concentrations or renal clearance of methotrexate in RA patients.
(2) The concurrent administration of 12.5, 25, or 50 mg rofecoxib and oral methotrexate (7.5 to 20 mg weekly) in RA patients is well tolerated.

REVIEWER'S COMMENT

- *The results obtained from placebo group are excluded in this review because they are not meaningful due to small sample size (N=3) and does not affect conclusions above.*
- *The effect of rofecoxib on methotrexate pharmacokinetics at the doses studied should not be extrapolated to infinity (∞) because the sponsor compared the geometric mean AUC_{0-24} rather than $AUC_{0-\infty}$ of 7-hydroxymethotrexate before and after each dose of rofecoxib.*
- *Based on this review, the labeling changes proposed by the sponsor are acceptable.*

REFERENCE 114: A 3-PART, 2-PERIOD, DOUBLE-BLIND, CROSSOVER STUDY TO INVESTIGATE THE EFFECT OF ORAL DOSES OF ROFECOXIB 12.5, 25, AND 50 MG ON THEOPHYLLINE PHARMACOKINETICS IN HEALTHY MALE VOLUNTEERS.

BACKGROUND

The sponsor reported three in vitro studies regarding the ability of rofecoxib to inhibit CYP1A2 activity. In the first 2 studies, rofecoxib and three metabolites were shown not to be rapid inhibitors of CYP1A2 activity. The third study demonstrated that rofecoxib was a modest inhibitor of CYP1A2. In earlier rofecoxib/warfarin interaction trials, the AUC of R(+) warfarin increased by a mean of 40 to 50%. R(+) warfarin is metabolized by CYP1A2 as well as other CYP and cytosolic enzymes. The biochemical mechanism of the increase in R(+) warfarin plasma concentration was unexplained. Therefore, this clinical study was conducted to assess the effects of rofecoxib on the metabolism of theophylline as a probe drug for cytochrome P-450 1A2 (CYP1A2) activity.

OBJECTIVES

(1) To investigate the influence of 7 days of rofecoxib 12.5, 25, and 50 mg on plasma concentrations of theophylline following a single oral dose of theophylline.
(2) To assess the tolerability of rofecoxib and theophylline taken concomitantly.

STUDY DESIGN

This study consisted of three parts. Each part was a randomized, double-blind, placebo-controlled, 2-period, crossover study to investigate the influence of rofecoxib on the pharmacokinetics of a single dose of oral theophylline. In each part, there were 2 periods during which each of the 12 subjects received either 12.5, 25 or 50 mg rofecoxib, or matching placebo once daily in the morning for 7 days. On the morning of Day 6 of each treatment period, each subject received a single oral dose of theophylline 300 mg. Blood samples were collected through 48 hours postdose (predose, 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 9, 12, 16, 24, 30, 36, and 48 hours postdose) for analysis of theophylline concentrations in plasma. There was a washout of at least 14 days between theophylline doses. Trough blood samples for rofecoxib were obtained predose Days 1 through 6 in each period. Blood and urine samples were obtained for safety assessment. Adverse experiences were monitored throughout the study.

Inclusion/Exclusion Criteria: Only male subjects were included in this study because some reports showed a possible influence of the menstrual cycle on the pharmacokinetics of theophylline. Subjects who were on NSAIDs, currently smoking, or habitually and heavily consuming coffee or caffeinated beverages were excluded. These and other inclusion/exclusion criteria are appropriate to achieve the study objectives.

METHODS

Study Drugs: Rofecoxib 12.5, 25, and 50 mg tablets (Batch No. MR-3475, MR-3481, and MR-3755, respectively) and corresponding placebo (MR-3551, MR-3529, and MR-3760,

respectively) were used. Theophylline was given as 3 x 100-mg Slo-Phyllin tablets (Rhone-Poulenc, Collegeville, PA).

Diet: Subjects were asked to refrain from the consumption of grapefruit juice, all caffeine-containing food or beverages, chocolate, charcoal grilled meats, and cruciferous vegetables such as broccoli, brussels sprouts, and cauliflower, for at least 48 hours prior to the theophylline dose and until the last blood sample for theophylline was obtained in each period. On the days of the theophylline dosing, the subjects fasted from all food and drink, except water, from midnight the evening before dosing. Subjects were also asked to avoid excess alcohol or strenuous physical activity for the duration of the study and follow-up period.

Evaluation Criteria: The effect of rofecoxib at steady state at the dose levels of 12.5, 25, and 50 mg on the single-dose theophylline pharmacokinetic parameters area under the concentration curve ($AUC_{0-\infty}$), maximum concentration (Cmax), time to maximum concentration (Tmax), and apparent terminal half-life ($t_{1/2}$) was compared with placebo. Safety and tolerability of theophylline when administered with rofecoxib was evaluated by adverse experiences and changes in the laboratory data.

Statistical Analysis: For each dose level of rofecoxib (12.5, 25, and 50 mg), a separate analysis of variance (ANOVA) model for a 2-period, crossover design was used to compare single-dose theophylline pharmacokinetic parameters ($AUC_{0-\infty}$, Cmax, Tmax, and $t_{1/2}$) for differences between the effects at steady state of rofecoxib and placebo. To assess the magnitude of differences between rofecoxib plus theophylline versus placebo plus theophylline, the geometric mean ratio (GMR) for theophylline $AUC_{0-\infty}$ and Cmax along with their 90% confidence intervals (CIs) were calculated. If the 90% CI at the given dose of rofecoxib for the theophylline $AUC_{0-\infty}$ GMR was contained within ⟮ ——— , then it was concluded that rofecoxib at steady state at the given dose had no significant effect on the $AUC_{0-\infty}$ single-dose administration of theophylline.

RESULTS

A total of 36 healthy men aged between 20 and 41 years old (mean, 25.3 years) was entered in this study. There were 25 whites, 4 blacks and 7 Asians. Thirty-five subjects completed the study; one subject withdrew consent and was not replaced.

Pharmacokinetics: Mean plasma concentrations for theophylline on Day 6 with rofecoxib 12.5, 25, and 50 mg once a day and placebo are shown in Figure 1, Figure 2, and Figure 3, respectively.

Figure 1

Mean Plasma Concentrations of Theophylline in Healthy Subjects Administered a Single Oral Dose of Theophylline on Day 6 of a 7-Day Course of Rofecoxib 12.5 mg Once a Day or Placebo

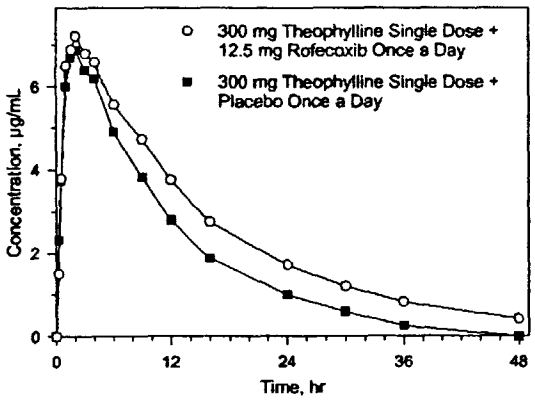


Figure 2

Mean Plasma Concentrations of Theophylline in Healthy Subjects Administered a Single Oral Dose of Theophylline on Day 6 of a 7-Day Course of Rofecoxib 25 mg Once a Day or Placebo

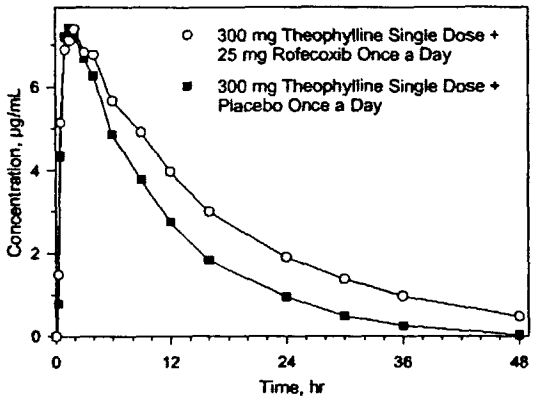
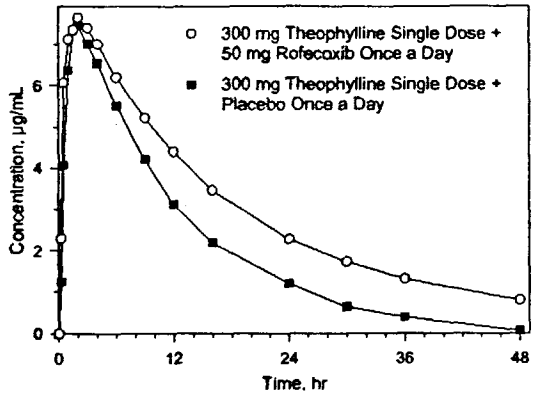


Figure 3

Mean Plasma Concentrations of Theophylline in Healthy Subjects Administered a Single Oral Dose of Theophylline on Day 6 of a 7-Day Course of Rofecoxib 50 mg Daily or Placebo



The following table provides the summary statistics for the single-dose pharmacokinetic parameters of theophylline when administered concomitantly after multiple-dose administrations with (12.5, 25, 50 mg) rofecoxib or placebo (N=12).

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	$AUC_{(0-\infty)}$ (µg•hr/mL)	C_{max} (µg/mL)	T_{max} (hr)	$t_{½}$ (hr)
Rofecoxib 12.5-mg Results (Part II)				
Rofecoxib (12.5 mg) + theophylline	120.5±35.4†	7.58±1.49†	1.48 ———	10.10±2.06§
Placebo + theophylline	87.3±23.6†	7.61±2.16†	1.52 ———	7.20±1.50§
Approximate within-subject CV (%)	7.02‖	16.95‖		
GMR (rofecoxib [12.5 mg]/placebo)	1.38	1.00		
(90% CI of GMR)	(1.31, 1.45)	(0.88, 1.13)		
Rofecoxib 25-mg Results (Part III)				
Rofecoxib (25 mg) + theophylline	130.5±41.2†	7.82±1.94†	1.50 ———	10.89±1.89§
Placebo + theophylline	86.3±27.1†	7.67±1.59†	1.50 ———	6.87±1.45§
Approximate within-subject CV (%)	6.81‖	7.75‖		
GMR (rofecoxib [25 mg]/placebo)	1.51	1.02		
(90% CI of GMR)	(1.43, 1.59)	(0.96, 1.08)		
Rofecoxib 50-mg Results (Part I)				
Rofecoxib (50 mg) + theophylline	156.1±34.4†	8.35±2.33†	1.29 ———	13.08±1.97§
Placebo + theophylline	97.3±26.5†	7.83±1.98†	1.50 ———	7.55±1.63§
Approximate within-subject CV (%)	9.62‖	12.00‖		
GMR (rofecoxib [50 mg]/placebo)	1.60	1.07		
90% CI of GMR	(1.49, 1.72)	(0.98, 1.17)		

† Geometric mean ± back-transformed standard deviation.
‡ Median (minimum, maximum).
§ Harmonic mean ± jackknife standard deviation.
‖ Root mean square error on the log scale • 100.
CV = Coefficient of variation.
GMR = Geometric mean ratio.

Geometric means of theophylline $AUC_{0-\infty}$ when theophylline 300 mg was administered with 12.5 mg rofecoxib and placebo were 120.5 and 87.3 µg·hr/mL, respectively. The difference between treatments was significant ($p < 0.001$). The corresponding GMR (rofecoxib/placebo) for theophylline $AUC_{0-\infty}$ was 1.38, with a corresponding 90% CI of [1.31, 1.45], and was not contained within the prespecified clinically significant comparability bounds of ———]. The estimated effects of the 25- and 50-mg doses of rofecoxib on the theophylline $AUC_{0-\infty}$ GMR [90% CI] were 1.51 [1.43, 1.59] and 1.60 [1.49, 1.72], respectively. Thus, all studied doses of rofecoxib have a clinically important interaction with theophylline with respect to $AUC_{0-\infty}$.

Geometric means of theophylline Cmax when theophylline 300 mg was administered with 12.5 mg rofecoxib and placebo were 7.58 and 7.61 µg/mL, respectively. The difference between treatments was not significant ($p > 0.200$). The corresponding GMR for theophylline Cmax was 1.00 [0.88, 1.13]. For the 25- and 50-mg dose comparisons, the GMR was 1.02 [0.96, 1.08] and 1.07 [0.98, 1.17], respectively. Thus, rofecoxib at the doses studied did not significantly affect theophylline Cmax when a single dose of theophylline was given.

The median theophylline Tmax values when administered with rofecoxib (12.5 mg) and placebo were 1.48 and 1.52 hours, respectively, and the difference between treatments was not significant ($p > 0.200$). There were also similar trends in higher rofecoxib doses (25 and 50 mg). Thus, none of the between-treatment comparisons were significantly different ($p > 0.200$).

The theophylline harmonic mean t½ value for rofecoxib (12.5 mg) plus theophylline (10.10 hours) was significantly longer than placebo plus theophylline (7.20 hours, $p < 0.001$). Similarly, after the multiple-dose administrations of rofecoxib at 25 and 50 mg, the theophylline harmonic mean t½ value was significantly longer than after placebo; 10.89 hours versus 6.87 and 13.08 hours versus 7.55 hours, respectively (both p values < 0.001).

Clearance of theophylline was lower in subjects administered 7-day courses of rofecoxib as evidenced by higher AUC and longer t½ values as compared with those administered placebo (the sponsor showed no data on this). Geometric means of theophylline clearance when theophylline 300 mg was administered with 12.5 mg rofecoxib and placebo were 41.5 and 57.3 mL/min, respectively. The corresponding GMR for theophylline clearance was 0.72, with a corresponding 90% CI of [0.69, 0.76]. At 25 and 50 mg doses, the geometric means were 38.3 versus 57.9 and 32.0 versus 51.4 mL/min, respectively. The estimated effects of the 25- and 50-mg doses of rofecoxib on the theophylline clearance GMR [90% CI] were 0.66 [0.63, 0.70] and 0.63 [0.58, 0.67], respectively. The mean trough plasma concentrations of rofecoxib still showed some increasing trend on Days 5 to 6 for doses of 12.5 and 25 mg (linear p-values, 0.040 and 0.034, repectively).

Overall, this study indicates that dosing with rofecoxib 12.5 through 50 mg interferes with the metabolic activity of CYP1A2 as expressed in the elimination of oral theophylline. The systemic absorption of theophylline seems to be little influenced by rofecoxib since no effect of dosing with the latter drug was observed on theophylline Cmax or Tmax.

Safety: Twenty-two subjects had a total of 35 clinical adverse experiences; 5 were recorded prior to the start of test drugs, of which 34 were considered definitely not related to study drug by the investigator. None were serious. One subject had a first degree AV block at the poststudy electrocardiogram (ECG) examination that was recorded as an adverse experience. After consultation with a cardiologist, it was judged that this was a normal variant for a young subject who exercises regularly and was not related to the test drug.

CONCLUSIONS

(1) Rofecoxib 12.5, 25, and 50 mg once daily moderately increases the theophylline plasma concentrations (increase in single-dose $AUC_{0-\infty}$ by 38 to 60%) in association with a prolonged elimination half-life. These data support inhibition by rofecoxib of CYP1A2.
(2) Based on pharmacokinetic data, theophylline plasma concentrations should be monitored when rofecoxib treatment is initiated or changed.

REVIEWER'S COMMENT

- *Considering the trends of rofecoxib trough concentrations, theophylline was given in this study near steady state concentrations of rofecoxib.*
- *Even though an increase in theophylline Cmax was not detected in this single dose study, it can be seen after multiple doses due to prolonged $t_{1/2}$ and resulting accumulation.*
- *According to the data and analysis provided, the sponsor's conclusions and corresponding labeling changes are acceptable.*

Reference 107:
An Open-Label, Multiple-Dose Study to Investigate the Influence of Moderate Hepatic Insufficiency on the Pharmacokinetics of MK–0966 (VIOXX™, ROFECOXIB)

Objectives:
(1) To compare the plasma concentration profile and pharmacokinetic parameters of rofecoxib following single- and multiple-dose administration of rofecoxib 12.5-mg tablets to moderate hepatic insufficiency patients with that of the control subjects. (2) To evaluate the safety and tolerability of multiple oral dose administration of rofecoxib 12.5-mg tablets in patients with moderate hepatic insufficiency and healthy subjects.

Study Design:
This was an open-label study comparing the pharmacokinetics of multiple oral doses of rofecoxib in patients with moderate hepatic insufficiency (9M/1F; Age: 52.8±9.1 yrs; Wt: 86.2±11.1 kg; Ht: 175.0±9.3 cm) to healthy control subjects (9M/1F; Age: 52.3±9.8 yrs; Wt: 82.2±9.1 kg; Ht: 171.2±8.1 cm) matched for age, gender, and body surface area (weight, height). Ten patients with moderate hepatic insufficiency (Child-Pugh's score: 7-9) and 10 healthy matched control subjects were enrolled and completed the study. Each patient/control subject received 12.5 mg rofecoxib once daily for 10 days. Treatment on Days 1 and 10 was administered with water in the fasted state.

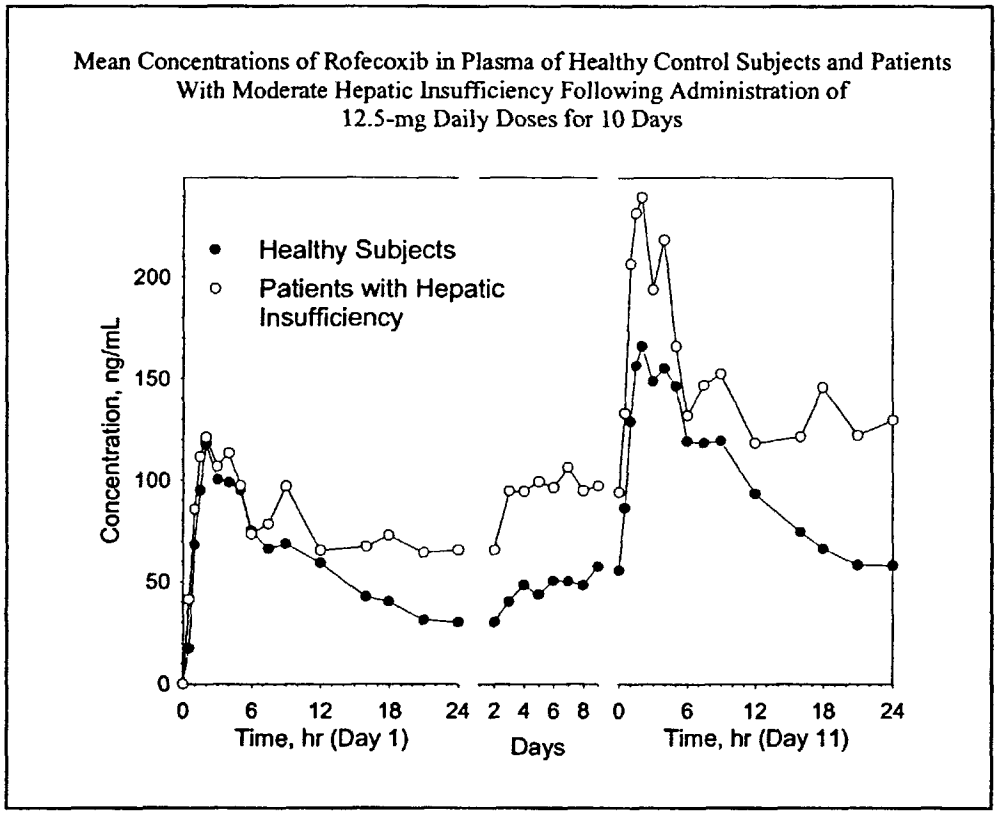
Child-Pugh Grade							
AN	Ascites	Neurologic	Prothrombin	Bilirubin	Albumin	Score	Class
011						7	Moderate
012						7	Moderate
013						9	Moderate
014						8	Moderate
015						8	Moderate
016						7	Moderate
017						7	Moderate
018						8	Moderate
019						8	Moderate
020						7	Moderate
Ascites: 1=absent; 2=slight; 3=moderate.							
Encephalopathy (grade): 1=none; 2=1 or 2; 3=3 or 4.							
Prothrombin times (secs over control): 1=<4; 2=4 to 6; 3=>6.							
Serum bilirubin (mg/100 mL): 1=<2; 2=2 to 3; 3=>3.							
Serum albumin (g/L): 1=>35; 2=28 to 35; 3=<28.							

Sampling:
Blood samples were collected at pre-dose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7.5, 9, 12, 16, 18, 21 and 24 hours postdose following the 1 st and 10 th dose. Predose blood (trough) samples for plasma rofecoxib concentration were obtained daily.

Assay

Results

The mean plasma rofecoxib concentrations throughout the time course of the study for the moderate hepatic patients and healthy subjects are shown in Figure 1. Based on trough concentration data, steady state was reached before Day 10 for both healthy subjects and patients with hepatic insufficiency. The median trough concentraiton on Day 10 was 99.5 ng/mL (range: ——— ng/mL) for the moderate hepatic insufficiency patients and 22.9 ng/mL (range: —— ng/mL) for the healthy subjects.



Mean (±SD) pharmacokinetic parameter values for the healthy controls and hepatic insufficiency patients on both Day 1 and Day 10 are listed in the table below. The mean values listed include arithmetic mean, geometric mean (GM) and least square mean (LSM) from ANCOVA analysis. One hepatic impairment patient (Subject #AN016) had an accumulation T1/2 of 4.6 hrs which is much shorter than that even for healthy subjects and, therefore, was excluded in the analyses described below. The sponsor, however, did provide results with this subject included in the analyses, which showed consistent findings. There is a statistically significant difference

($p<0.05$) in steady-state Cmax and AUC between the moderate hepatic insufficiency patients and healthy controls.

Table: Mean (±SD) PK Parameter Values in Healthy Subjects and Moderate Hepatic Impairment Patients

PK Parameter	Healthy Controls (N=10)				Moderate Hepatic InsufficiencyPatients (N=9)			
	Cmax (ng/mL)	Tmax (hr)	AUC_{0-24} (ng.h/mL)	T1/2	Cmax (ng/mL)	Tmax (hr)	AUC_{0-24} (ng.h/mL)	T1/2
Day 1								
Mean*	127.9	2.20	1397	-	144.2	2.72	1860	-
SD	36.9	1.01	379	-	47.9	1.35	701	-
LSM	121	-	1330	-	141		1762	-
Day 10								
Mean*	176.3	2.46	2349	16.4*	259.8	2.17	3497	20.8**
SD	67.3	1.11	994	-	104.7	0.86	1225	-
LSM	162	-	2152	-	247	-	3325	-

*Arithmetic mean

**Harmonic mean of accumulation T1/2; calculated from the ratio of AUC values from Day 1 and Day 10.

Based on ANCOVA analyses, the least square mean ratio (LSMR), its corresponding 90% confidence intervals and intersubject variability (as %CV) are given below. At steady state, patients with moderate hepatic impairment had approximately 50% higher Cmax and AUC. Tmax in both groups were comparable. Elimination of rofecoxib is slower in patients with moderate hepatic insufficiency with a mean accumulation half-life of 20.8 hours as compared to 16.4 hours in healthy controls (see table above).

Table: Summary Statistics for PK Parameters (Hepatic Patients vs. Healthy Controls)

Parameter	Cmax			AUC_{0-24}		
	LSMR	90% CI	%CV	LSMR	90% CI	%CV
Day 1	1.17	0.91-1.50	28.9	1.32	0.98-1.79	34.9
Day 10	1.53	1.11-2.09	36.8	1.55	1.15-2.07	34.3

Sponsor's conclusion:

At steady state, patients with moderate hepatic impairment had approximately a 50% higher Cmax and AUC. The sponsor considers this increase not clinically significant since oral doses up to 125 mg for up to 6 weeks was generally well tolerated in previous studies.

Comment:

The individual data were examined. Only one out of the 10 patients in this study had a Child-Pugh score of 9. The mean AUC for the 4 patients with a Child-Pugh score of 8 was approximately 20% higher than that for the 4 patients with a score of 7. The variability in patients with a score of 7 was high (CV: 56.7%). The one patient with a score of 9 had AUC value ranked in the middle among the patients with a score of 8. In view of this, it is considered unnecessary to make separate dosage recommendation for the three Child-Pugh scores. Because of the concern about cardiovascular adverse events and the increased rofecoxib concentrations observed in moderate hepatic impairment patients, we recommend that these patients start with the lowest possible dose with careful monitoring of signs and symptoms of adverse events.

Patients with severe hepatic insufficiency have not been studied. Use of rofecoxib in these patients is not recommended.

Appendix: Sponsor's Proposed Label Changes

I. Package Insert

A) "CLINICAL PHARAMCOLOGY" section

1) Under "Special Populations"

Hepatic Insufficiency

A single-dose[1] pharmacokinetic study in mild (Child-Pugh score ≤6) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. A pharmacokinetic study[2] in patients with moderate (Child-Pugh score 7-9) hepatic insufficiency indicated that mean rofecoxib

[ ]

Patients with severe hepatic insufficiency have not been studied.

2) Under "Drug Interactions"

B. "PRECAUTION" section

1) Under "General"

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with VIOXX. Use of VIOXX is not recommended in patients with severe hepatic insufficiency (see *Pharmacokinetics, Special Populations*). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), VIOXX should be discontinued.

2) Under "Drug Interactions"

Methotrexate: VIOXX 12.5, 25, and 50 mg, each dose administered once daily for 7 days,[8] had no effect on the plasma concentration of methotrexate as measured by $AUC_{0\text{-}24h}$[9] in patients receiving single weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis.[10] At higher than recommended doses,[11] VIOXX 75 mg administered once daily for 10 days increased plasma concentrations by 23% as measured by $AUC_{0\text{-}24hr}$ in patients receiving methotrexate 7.5 to 15 mg/week for rheumatoid arthritis. –At 24 hours postdose, a similar proportion of patients treated with methotrexate alone (94%) and subsequently treated with methotrexate co-administered with 75 mg of rofecoxib (88%) had methotrexate plasma concentrations below the measurable limit (5 ng/mL).

[ ]

Oral Contraceptives: Rofecoxib did not have any clinically important effect on the pharmacokinetics of ethinyl estradiol and norethindrone.

Prednisone/prednisolone: Rofecoxib did not have any clinically important effect on the pharmacokinetics of prednisolone or prednisone.

Rifampin: Co-administration of VIOXX with rifampin 600 mg daily, a potent inducer of hepatic metabolism, produced an approximate 50% decrease in rofecoxib plasma concentrations. Therefore, a starting daily dose of 25 mg of VIOXX should be considered for the treatment of osteoarthritis when VIOXX is co-administered with potent inducers of hepatic metabolism.

Theophylline: VIOXX 12.5, 25, and 50 mg administered once daily for 7 days[15] increased plasma theophylline concentrations ($AUC_{(0-\infty)}$) by 38 to 60% in healthy subjects[16] administered a single 300 mg dose of theophylline.[17] Adequate monitoring of theophylline plasma concentrations should be considered when therapy with VIOXX is initiated or changed in patients receiving theophylline.[18]

These data suggest that rofecoxib may produce a modest inhibition of cytochrome P450 (CYP) 1A2.[19] Therefore, there is a potential for an interaction with other drugs that are metabolized by CYP1A2 (e.g., amitriptyline, tacrine, and zileuton).[20]

II. Patient Information

Can I take VIOXX with other medicines?

Tell your doctor about all of the other medicines you are taking or plan to take while you are on VIOXX, even other medicines that you can get without a prescription. Your doctor may want to check that your medicines are working properly together if you are taking other medicines such as:

- warfarin (a blood thinner)
- theophylline (a medicine used to treat asthma)
- rifampin (an antibiotic)
- ACE inhibitors (medicines used for high blood pressure and heart failure).

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/s/

Sue Chih Lee
12/10/01 11:03:00 AM
BIOPHARMACEUTICS

Hard copy already signed off. Please sign off electronically.

Jiang-Ik Lee
12/10/01 11:11:00 AM
PHARMACOLOGIST

Dennis Bashaw
12/10/01 03:30:34 PM
BIOPHARMACEUTICS

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