PRODUCT MONOGRAPH

VIOXX®

rofecoxib tablets

12.5, 25 and 50 mg

VIOXX®

rofecoxib oral suspension

12.5 mg/5 mL and 25 mg/5 mL

THERAPEUTIC CLASSIFICATION

Anti-inflammatory Analgesic Agent

MERCK FROSST CANADA & CO.
KIRKLAND, QUEBEC, CANADA

Initial Date of Preparation:
October 20, 1999

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August 11, 2004

Control #092249

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ACTION AND CLINICAL PHARMACOLOGY

VIOXX® (rofecoxib) is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic activities in animal models. At therapeutic doses, VIOXX® is an orally active cyclooxygenase-2 (COX-2) selective inhibitor. At therapeutic concentrations, VIOXX® does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

Cyclooxygenase is responsible for the generation of prostaglandins, which are potent biological mediators involved in diverse physiologic functions as well as in pathologic conditions. Two isoforms of cyclooxygenase have been identified: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is constitutively expressed and enzymatically active in various tissues, including the stomach, intestines, and kidneys, and in platelets. The prostaglandins produced by COX-1 play key roles in the maintenance of physiological functions such as platelet aggregation and are among the factors that maintain the GI mucosal barrier. Inhibition of COX-1 has been associated with gastric damage. COX-2 is constitutively expressed and plays a physiological role in a limited number of tissues, including the brain, kidney and female reproductive tract.

In addition, inhibition of COX-2 reduces the formation of systemic (and therefore possibly endothelial) prostacyclin. Both COX-1 and COX-2 are important for normal renal function and inhibition of these enzymes has been associated with renal toxicity. COX-2 is the inducible isoform of the enzyme that has been shown to be up-regulated by proinflammatory stimuli. COX-2 is primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. Selective inhibition of COX-2 by VIOXX® decreases these clinical signs and symptoms without influencing gastrointestinal integrity or platelet function at recommended therapeutic doses (see PHARMACOLOGY, Mechanism of Action).

Pharmacokinetics

Absorption

The mean oral bioavailability of VIOXX® at therapeutically recommended doses of 12.5, 25, and 50 mg is approximately 93%. The geometric mean (95% CI) for the area under the curve (AUC) and peak plasma level (C_{max}) following a single 25 mg dose were 3186 (95% CI: [2698, 3763]) ng•hr/mL and 185 (95% CI: [137, 250]) ng/mL, respectively. Both C_{max} and AUC are roughly dose proportional across the clinical dose range. At doses greater than 50 mg, there is a less than proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. With multiple dosing, steady-state conditions are reached by Day 4. The geometric mean (95% CI) $AUC_{0\text{-}24hr}$ and C_{max} at steady state after multiple doses of 25 mg rofecoxib was 3867 (95% CI: [3212, 4656]) ng•hr/mL and 305 (95% CI: [248, 376]) ng/mL, respectively. The accumulation factor based on geometric means was 1.67.

VIOXX® tablets 12.5 mg and 25 mg are bioequivalent to VIOXX® oral suspension 12.5 mg/5 mL and 25 mg/5 mL, respectively.

Food and Antacid Effects

Food had no significant effect on either the peak plasma concentration (C_{max}) or extent of absorption (AUC) of rofecoxib when VIOXX® tablets were taken with a high fat meal. The time to peak plasma concentration (T_{max}), however, was delayed by 1 to 2 hours.

The food effect on the suspension formulation has not been studied. VIOXX® tablets can be administered without regard to timing of meals.

There was a 13% and 8% decrease in AUC when VIOXX® was administered with calcium carbonate antacid and magnesium/aluminum antacid to elderly subjects, respectively. There was an approximate 20% decrease in C_{max} of rofecoxib with either antacid.

Distribution

Rofecoxib is approximately 87% bound to human plasma protein over the range of concentrations of 0.05 to 25 µg/mL. The apparent volume of distribution at steady state (V_{dss}) is approximately 91 L following a 12.5 mg dose and 86 L following a 25 mg dose.

Rofecoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

Metabolism of rofecoxib is primarily mediated through reduction by cytosolic enzymes. The principal metabolic products are the *cis*-dihydro and *trans*-dihydro derivatives of rofecoxib, which account for nearly 56% of recovered radioactivity in the urine. An additional 8.8% of the dose was recovered as the glucuronide of the hydroxy derivative, a product of oxidative metabolism. The biotransformation of rofecoxib and this metabolite is reversible in humans to a limited extent (<5%). These metabolites are inactive as COX-1 or COX-2 inhibitors.

Cytochrome P450 plays a minor role in metabolism of rofecoxib. Inhibition of CYP 3A activity by administration of ketoconazole 400 mg daily does not affect rofecoxib disposition. However, induction of general hepatic metabolic activity by administration of the non specific inducer rifampin 600 mg daily produces a 50% decrease in rofecoxib plasma concentrations (see PRECAUTIONS, Drug Interactions).

Excretion

Rofecoxib is eliminated predominantly by hepatic metabolism with little (<1%) unchanged drug recovered in the urine. Following a single radiolabeled dose of 125 mg, approximately 72% of the dose was excreted into the urine as metabolites and 14% in the feces as unchanged drug.

The effective half-life (based on steady-state levels) was approximately 17 hours. The plasma clearance after 12.5 and 25 mg doses was approximately 141 and 120 mL/min, respectively.

Special Populations

Gender

The pharmacokinetics of rofecoxib are comparable in men and women.

Geriatric

After a single dose of 25 mg VIOXX® in elderly subjects (over 65 years old) a 34% increase in AUC was observed as compared to the young subjects. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX® should be initiated at the lowest recommended dose.

Race

Meta-analysis of pharmacokinetic studies has suggested a slightly (10-15%) higher AUC of rofecoxib in Blacks and Hispanics as compared to Caucasians. No dosage adjustment is necessary on the basis of race.

Hepatic Insufficiency

A single-dose pharmacokinetic study in mild (Child-Pugh score $\leq$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 mean rofecoxib steady-state AUC was increased

55% relative to healthy subjects. Patients with severe hepatic insufficiency have not been studied.

Renal Insufficiency

In a study (N=6) of patients with end stage renal disease undergoing dialysis, peak rofecoxib plasma levels and AUC declined 18% and 9%, respectively, when dialysis occurred four hours after dosing. When dialysis occurred 48 hours after dosing, the elimination profile of rofecoxib was unchanged. While renal insufficiency does not influence the pharmacokinetics of rofecoxib, use of VIOXX® in advanced renal disease is not recommended at present because no safety information is available regarding the use of VIOXX® in these patients (see WARNINGS, Advanced Renal Disease, PRECAUTIONS, Renal Function, and DOSAGE AND ADMINISTRATION).

Pediatric Patients

The pharmacokinetics of rofecoxib in pediatric patients have not been studied.

Clinical Studies

Osteoarthritis

Six double-blind, randomized clinical trials of VIOXX®, lasting from 6 to 86 weeks, were carried out in 4035 patients with osteoarthritis of the knee and hip, including approximately 400 patients ≥80 years of age. VIOXX® 12.5 and 25 mg administered once daily demonstrated efficacy comparable to 150 mg (50 mg three times a day) of diclofenac and 2400 mg (800 mg three times a day) of ibuprofen and superior to placebo. Patients showed clinically significant improvements in the signs and symptoms of osteoarthritis, including reduction in pain, joint stiffness, joint tenderness, and physical disability. Additionally, patients' assessment of response to study medication and investigators' assessment of the patients' disease status were similarly comparable to diclofenac and ibuprofen and superior to placebo. Clinical efficacy was demonstrated within one week , the first evaluation timepoint, and continued for the duration of the studies up to one year. Doses above 25 mg daily provided no additional clinical benefit. As a measure of effect on cartilage, at one year, joint space narrowing (assessed

radiographically) of the knee in patients treated with VIOXX® (12.5 and 25 mg daily) was similar to that seen in patients treated with diclofenac (150 mg daily).

Rheumatoid Arthritis (RA)

VIOXX® has demonstrated significant reduction in joint tenderness/pain and joint swelling compared to placebo. VIOXX® was evaluated for the treatment of the signs and symptoms of RA in two 12-week placebo- and active-controlled clinical trials that enrolled a total of approximately 2000 patients. VIOXX® was shown to be superior to placebo on all primary endpoints (number of tender joints, number of swollen joints, patient and physician global assessments of disease activity). In addition, VIOXX® was shown to be superior to placebo using the American College of Rheumatology 20% (ACR20) Responder Index, a composite of clinical, laboratory, and functional measures of RA. VIOXX® 25 mg once daily and naproxen 500 mg twice daily showed generally similar effects in the treatment of RA. The beneficial effects were maintained over the 12-week treatment period. A 50 mg dose once daily of VIOXX® was also studied; however, no significant additional efficacy was seen compared to the 25 mg dose.

Analgesia, Including Primary Dysmenorrhea

In clinical studies, VIOXX® relieved pain in acute analgesic models of post-operative dental pain, post-orthopedic surgical pain, and primary dysmenorrhea. In single-dose clinical studies, the analgesic effect of a 50 mg dose of VIOXX® was generally similar to a maximum analgesic dose of naproxen sodium (550 mg) or ibuprofen (400 mg). The onset of analgesia with the single 50 mg dose of VIOXX® occurred within 45 minutes and persisted for as long as 24 hours after dosing. In multiple-dose clinical studies, lasting up to 5 days, of post-orthopedic surgical pain and pain from primary dysmenorrhea, after an initial 50 mg dose, 25 to 50 mg once daily of VIOXX® was effective in relieving pain.

Gastrointestinal Safety

Endoscopy Studies

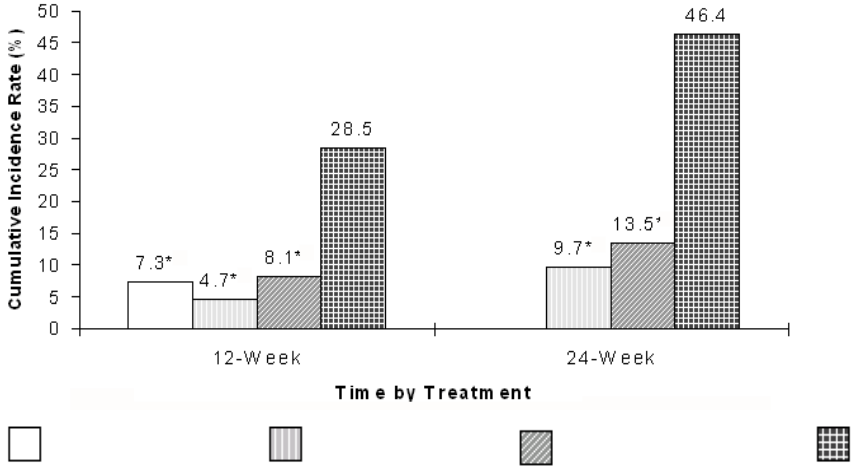
Upper Endoscopy in Patients with Osteoarthritis

Two identical (U.S. and Multinational) endoscopy studies in a total of 1516 patients were conducted to compare the percentage of patients who developed endoscopically detectable gastroduodenal ulcers with VIOXX® 25 mg daily or 50 mg daily, ibuprofen 2400 mg daily, or placebo. Patients who were 50 years of age and older with osteoarthritis and no ulcers at baseline were evaluated by endoscopy after weeks 6 (for safety), 12, and 24 of treatment. The placebo-treatment group was discontinued at week 16 by design. In each of the U.S. and the Multinational studies, the primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks. Treatment with VIOXX® 25 mg daily or 50 mg daily resulted in significantly lower percentages of patients with gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. See Figure 1 for the combined analysis showing cumulative incidences of ulcers at 12 weeks (which includes data from the 6- and 12-week endoscopies) and 24 weeks (which includes data from the 6-, 12-, and 24-week endoscopies).

In a predefined, combined analysis of the two trials at 12 weeks of treatment, the percentages of patients with endoscopically detected gastroduodenal ulcers were similar between VIOXX® 25 mg daily, VIOXX® 50 mg daily, and placebo.

Figure 1

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥3 mm† with Detectable Depth Intention-to-Treat



Placebo

VIOXX® 25mg

VIOXX® 50

				mg Ibuprofen 2400 mg
n=340	n=373	n=360	n=354	

* p <0.001 versus Ibuprofen 2400 mg
† Results of analyses using a ≥5 mm gastroduodenal ulcer endpoint were consistent.

The following patients at a higher risk for ulcers were included in the studies: patients with active *Helicobacter pylori* infection, baseline gastroduodenal erosions, and/or a prior history of perforation, ulcer or bleed (PUB). Five hundred twenty-six patients (34.7%) were 65 years of age and older. The advantage of VIOXX® was maintained in these higher risk subgroups. Patients receiving acetylsalicylic acid (ASA), including low-dose ASA for cardiovascular prophylaxis, were not enrolled in these studies.

Upper Endoscopy in Patients with Rheumatoid Arthritis

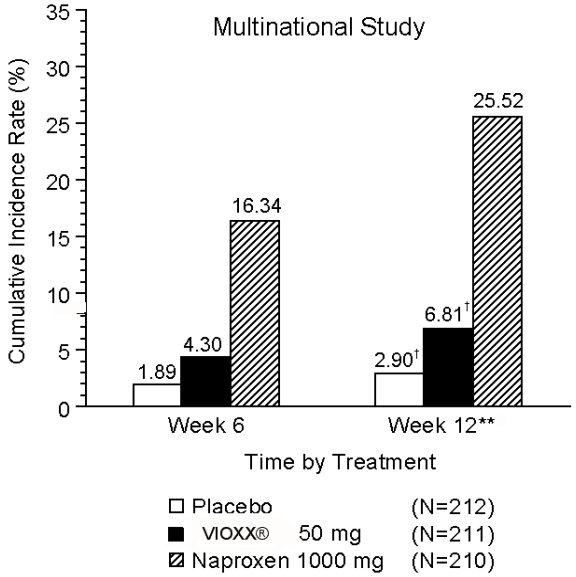
A 12-week, double-blind, placebo- and active-controlled endoscopy study of 660 patients with RA was conducted to compare the percentage of patients who developed endoscopically detectable gastroduodenal ulcers with VIOXX® 50 mg once daily (twice the maximum dose recommended for chronic use), naproxen 500 mg twice daily, or placebo. Entry criteria for this study permitted enrollment of patients with active *Helicobacter pylori* infection, baseline gastroduodenal erosions, concomitant use of corticosteroids, prior history of an upper gastrointestinal perforation, ulcer, or bleed (PUB), and/or age ≥65 years. However, patients receiving ASA (including low-dose ASA for cardiovascular prophylaxis) were not enrolled in this study. Patients who were 18 years of age and older with RA and who had no ulcers at baseline were evaluated by endoscopy after 6 and 12 weeks of treatment.

Treatment with VIOXX® 50 mg once daily (twice the maximum dose recommended for chronic use) was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with naproxen 500 mg twice daily.

The advantage of VIOXX® was maintained in the following higher risk subgroups: patients with active *Helicobacter pylori* infection, patients with baseline gastroduodenal erosions, patients taking corticosteroids, patients with a prior history of a PUB, and elderly patients (65 years of age and older). See Figure 2 and the accompanying table for the results of this study.

Figure 2

Comparison to Naproxen
Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥3 mm* (Intention-to-Treat)



† p<0.001

versus naproxen 500 mg twice daily

* Results of analyses using a ≥5 mm gastroduodenal ulcer endpoint were consistent.

**The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

Endoscopic Gastroduodenal Ulcers at 12 weeks
Multinational Study

Treatment Group	Number of Patients With Ulcer/ Total Number of Patients	Cumulative Incidence Rate*	Ratio of Rates vs. Placebo	95% CI on Ratio of Rates
Placebo	6/212	2.90%	-	-
VIOXX® 50 mg	14/211	6.81%	2.35	(0.92, 6.00)
Naproxen 1000 mg	51/210	25.52%	8.8	(3.86, 20.07)

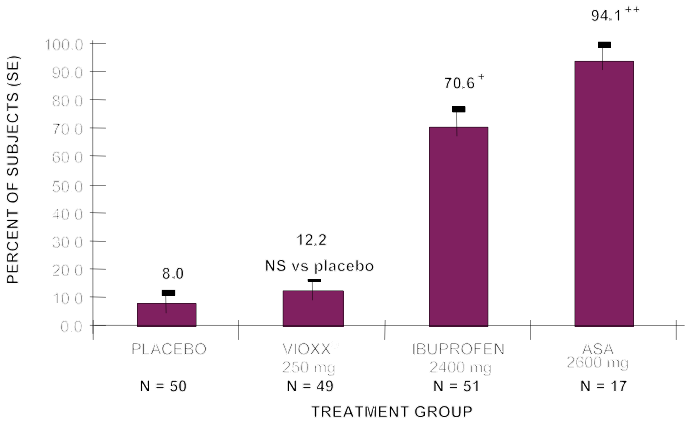
*by life table analysis

Upper Endoscopy in Healthy Subjects

In a separate study, 167 healthy subjects were evaluated by endoscopy after 7 days of treatment with VIOXX® 250 mg daily, ibuprofen 2400 mg daily, ASA 2600 mg daily, or placebo. No subjects had upper gastrointestinal mucosal abnormalities at baseline endoscopy. The gastroduodenal mucosa was evaluated using a predefined scale with a score ranging from 0 to 4; scores ≥ 2 corresponded to development of erosion and/or ulcer. Significantly fewer subjects treated with VIOXX® 250 mg daily (a dose 10 to 20-fold higher than that indicated for the treatment of osteoarthritis) developed endoscopically evident mucosal injury than subjects treated with ibuprofen 2400 mg daily or ASA 2600 mg daily. In addition, the number of subjects treated with VIOXX® who developed endoscopically evident mucosal injury was generally similar to placebo (Figure 3).

Figure 3

Percent of Subjects with Maximum Gastroduodenal Erosion Score ≥2



\+ p<0.001 vs placebo and VIOXX

++ p<0.001 vs placebo and VIOXX ; p=0.054 vs ibuprofen

SE = standard error

NS = not significant vs placebo

VIOXX® GI Clinical Outcomes Research (VIGOR) Study

Study Design

The VIGOR study was designed to evaluate the comparative GI safety of VIOXX® 50 mg once daily (twice the highest dose recommended for chronic use in OA) versus naproxen 500 mg twice daily (common therapeutic dose). The general safety and tolerability of VIOXX® 50 mg once daily versus naproxen 500 mg twice daily was also studied. VIGOR was a randomized, double-blind study (median duration of 9 months) in 8076 patients with rheumatoid arthritis (RA) requiring chronic NSAID therapy (mean age 58 years). Patients were not permitted to use concomitant ASA or other antiplatelet drugs. Patients with a recent history of myocardial infarction or stroke and patients deemed to require low-dose ASA for cardiovascular prophylaxis were to be excluded from the study. Fifty-six percent of patients used concomitant oral corticosteroids. The GI safety endpoints (confirmed by a blinded adjudication committee) included:

- PUBs-symptomatic ulcers, upper GI perforation, obstruction, major or minor upper GI bleeding.
- Complicated PUBs (a subset of PUBs)-upper GI perforation, obstruction or major upper GI bleeding.

Study Results

Gastrointestinal Safety in VIGOR

The VIGOR study showed a significant reduction in the risk of development of PUBs, including complicated PUBs in patients taking VIOXX® compared to naproxen (see Table 1).

Table 1

VIGOR-Summary of Patients with Gastrointestinal Safety Events[1]
COMPARISON TO NAPROXEN

GI Safety Endpoints	VIOXX® 50 mg daily (N=4047)[2] n[3] (Cumulative Rate[4])	Naproxen 1000 mg daily (N=4029)[2] n[3] (Cumulative Rate[4])	Relative Risk of VIOXX® compared to naproxen[5]	95% CI[5]
PUBs	56 (1.80)	121 (3.87)	0.46*	(0.33, 0.64)
Complicated PUBs	16 (0.52)	37 (1.22)	0.43*	(0.24, 0.78)

[1]As confirmed by an independent committee blinded to treatment, [2]N=Patients randomized, [3]n=Patients with events,
[4]Kaplan-Meier cumulative rate at end of study when at least 500 patients remained (approx. 10 1/2 months), [5]Based on Cox proportional hazard model

*p-value $\leq$0.005 for relative risk compared to naproxen

The risk reduction for PUBs and complicated PUBs for VIOXX® compared to naproxen (approximately 50%) was maintained in patients with or without the following risk factors for developing a PUB (Kaplan-Meier cumulative rate of PUBs at approximately 10½ months, VIOXX® versus naproxen, respectively): with a prior PUB (5.12, 11.47); without a prior PUB (1.54, 3.27); age 65 or older (2.83, 6.49); or younger than 65 years of age (1.48, 3.01). A similar risk reduction for PUBs and complicated PUBs (approximately 50%) was also maintained in patients with or without *Helicobacter pylori* infection or concomitant corticosteroid use.

Other Safety Findings: Cardiovascular Safety

The VIGOR study showed a higher incidence of adjudicated serious cardiovascular thrombotic events in patients treated with VIOXX® 50 mg once daily as compared to patients treated with naproxen 500 mg twice daily (see Table 2). This finding was largely due to a difference in the incidence of myocardial infarction between the groups (see Table 3) (see PRECAUTIONS, Cardiovascular Effects). Adjudicated serious cardiovascular events (confirmed by a blinded adjudication committee) included: sudden death, myocardial infarction, unstable angina, ischemic stroke, transient ischemic attack and peripheral venous and arterial thromboses.

Table 2

VIGOR-Summary of Patients with Serious Cardiovascular Thrombotic Adverse Events[1] Over Time COMPARISON TO NAPROXEN

Treatment group	Patients Randomized		4 Months[2]	8 Months[3]	10 ½ Months[4]
VIOXX® 50 mg	4047	Total number of events	17	29	45
		Cumulative Rate †	0.46%	0.82%	1.81%*
Naproxen 1000 mg	4029	Total number of events	9	15	19
		Cumulative Rate †	0.23%	0.43%	0.60%

[1] Confirmed by blinded adjudication committee,
[2] Number of patients remaining after 4 months were 3405 and 3395 for VIOXX® and naproxen respectively,
[3] Number of patients remaining after 8 months were 2806 and 2798 for VIOXX® and naproxen respectively,
[4] Number of patients were 531 and 514 for VIOXX® and naproxen respectively.
† Kaplan-Meier cumulative rate.
* p-value <0.002 for the overall relative risk compared to naproxen by Cox proportional hazard model

Table 3

VIGOR- Serious Cardiovascular Thrombotic Adverse Events[1]

	VIOXX® 50 mg N[2]=4047 n[3]	Naproxen 1000 mg N[2] =4029 n[3]
Any CV thrombotic event	45*	19
Cardiac events	28**	10
Fatal MI/Sudden death	5	4
Non-fatal MI	18**	4
Unstable angina	5	2
Cerebrovascular	11	8
Ischemic stroke	9	8
TIA	2	0
Peripheral	6	1

[1] Confirmed by blinded adjudication committee,
[2] N=Patients randomized,
[3] n=Patients with events.
* p-value <0.002 and ** p-value ≤0.006 for relative risk compared to naproxen by Cox proportional hazard model

For cardiovascular data from 2 long-term placebo-controlled studies, see PRECAUTIONS, Cardiovascular Effects.

Special Studies

Assessment of Fecal Occult Blood Loss in Healthy Subjects

To assess mucosal integrity throughout the gastrointestinal tract, fecal blood loss with VIOXX® 25 mg daily, VIOXX® 50 mg daily, ibuprofen 2400 mg daily, and placebo was compared in a study utilizing ^{51}Cr-tagged red blood cells in 67 healthy males. After 4 weeks of treatment with VIOXX® 25 mg daily or VIOXX ® 50 mg daily, there was no significant increase in the amount of fecal blood loss compared with placebo-treated subjects. In contrast, ibuprofen 2400 mg daily produced a significant increase in fecal blood loss as compared with placebo-treated subjects and subjects treated with VIOXX®.

Assessment of Intestinal Permeability in Healthy Subjects

As an additional measure of mucosal integrity in the small bowel, intestinal permeability with VIOXX® 25 mg daily, VIOXX® 50 mg daily, indomethacin 150 mg daily, and placebo was compared in a study utilizing ^{51}Cr-tagged EDTA in 30 healthy subjects. After 1 week of treatment with VIOXX® 25 mg daily or VIOXX® 50 mg daily, there was no significant increase in intestinal permeability compared with placebo-treated subjects. In contrast, indomethacin 150 mg daily produced a significant increase in intestinal permeability as compared with placebo-treated subjects and subjects treated with VIOXX®.

Platelet Function

Multiple doses of VIOXX® 12.5, 25, and up to 375 mg administered daily up to 12 days had no effect on bleeding time relative to placebo. Similarly, bleeding time was not altered in a single dose study with 500 or 1000 mg of VIOXX®. There was no inhibition of *ex vivo* arachidonic acid- or collagen-induced platelet aggregation with 12.5, 25 and 50 mg of VIOXX®. These findings are consistent with the COX-2 selectivity of rofecoxib.

ASA

At steady state, VIOXX® 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) ASA, as assessed by *ex vivo* platelet aggregation and serum TXB_2 generated in clotting blood (a biochemical marker of platelet activation) (see PRECAUTIONS, Drug Interactions).

Use with Acetylsalicylic Acid

As a selective inhibitor of COX-2, rofecoxib does not inhibit platelet function and can not substitute for ASA for protection against myocardial infarction. VIOXX® can be used with low-dose ASA. However, concomitant administration of low-dose ASA with VIOXX® may result in an increased rate of GI ulceration or other complications, compared to use of VIOXX® alone (see PRECAUTIONS, Drug Interactions, ASA).

In 3 six-week, double-blind, randomized efficacy and safety clinical trials, VIOXX® 12.5 mg (n=134) or 25 mg (n=27) was administered to osteoarthritic patients concomitantly with low-dose ASA (less than or equal to 325 mg daily) (N = 161). No clinically important differences in the overall incidence of clinical adverse experiences were noted for users of VIOXX® plus ASA *versus* VIOXX® alone.

INDICATIONS AND CLINICAL USE

VIOXX® (rofecoxib) is indicated for:

- Acute and chronic treatment of the signs and symptoms of osteoarthritis.
- Acute and chronic treatment of the signs and symptoms of rheumatoid arthritis in adults.
- Relief of pain in adults.
- Treatment of primary dysmenorrhea.

CONTRAINDICATIONS

VIOXX® (rofecoxib) is contraindicated in patients with known hypersensitivity to rofecoxib or any other component of VIOXX®.

VIOXX® should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking ASA or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, Anaphylactoid Reactions and PRECAUTIONS, Hypersensitivity Reactions).

Active peptic ulcer, active GI bleeding or active inflammatory disease of the bowel.

Significant hepatic impairment or active liver disease.

Severely impaired or deteriorating renal disease (creatinine clearance < 0.5 mL/sec: 30 mL/min). Individuals with lesser degrees of renal impairment are at risk of deterioration of their renal function when prescribed NSAIDs and must be monitored.

WARNINGS

Gastrointestinal System (GI)

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is

symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

To minimize the potential risk for an adverse GI event, the lowest effective dose should be used for the shortest possible duration. For high risk patients, alternate therapies that do not involve NSAIDs should be considered.

The risk of GI toxicity is not completely eliminated with VIOXX®. The results of the VIOXX® GI Clinical outcomes research (VIGOR) study demonstrate that in patients treated with VIOXX®, the risk of GI toxicity with VIOXX® 50 mg once daily is significantly less than with naproxen 500 mg twice daily (see ACTION AND CLINICAL PHARMACOLOGY, Clinical Studies, Gastrointestinal Safety, Clinical Upper GI Outcomes, VIOXX® GI Clinical Outcomes Research (VIGOR) Study).

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or gastrointestinal bleeding. Most spontaneous reports of fatal GI events are in elderly or debilitated patients and therefore special care should be taken in treating this population.

Studies have shown that patients with a *prior history of peptic ulcer disease and/or gastrointestinal bleeding* and who use NSAIDs, have a greater than 10-fold higher risk for developing a GI bleed than patients with neither of these risk factors. In addition to a past history of ulcer disease, pharmacoepidemiological studies have identified several other co-therapies or co-morbid conditions that may increase the risk for GI bleeding such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to VIOXX®. In post-marketing experience, rare cases of anaphylactic/anaphylactoid reactions and angioedema have been reported in patients receiving VIOXX®. VIOXX® should not be given to patients with the "aspirin triad". This symptom complex typically occurs in asthmatic patients who experience rhinitis with or without nasal polyps, or who exhibit severe, potentially fatal bronchospasm after taking ASA or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, Hypersensitivity Reactions). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

Advanced Renal Disease

No safety information is available regarding the use of VIOXX® in patients with advanced kidney disease. Therefore, treatment with VIOXX® is not recommended in these patients. If VIOXX® therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, Renal Function).

Cross-sensitivity

Patients sensitive to any one of the nonsteroidal anti-inflammatory drugs may be sensitive to any of the other NSAIDs also.

Aseptic Meningitis

In occasional cases, with some NSAIDs, the symptoms of aseptic meningitis (stiff neck, severe headaches, nausea and vomiting, fever or clouding of consciousness) have been observed. Patients with autoimmune disorders (systemic lupus erythematosus, mixed connective tissues diseases, etc.) seem to be predisposed. Therefore, in such patients, the physician must be vigilant to the development of this complication. In post-marketing experience, very rare cases of aseptic meningitis have been reported in patients.

Pregnancy

There are no adequate and well controlled studies in pregnant women.

As with other drugs known to inhibit prostaglandin synthesis, use of VIOXX® should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus.

VIOXX® should be used during the first two trimesters of pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use in Nursing Mothers

Rofecoxib is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the possible adverse effects of drugs that inhibit prostaglandin synthesis on nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Use in Children

Safety and effectiveness in pediatric patients have not been established.

PRECAUTIONS

General

VIOXX® (rofecoxib) cannot be expected to substitute for corticosteroids or to treat corticosteroid insufficiency. Abrupt discontinuation of corticosteroids may lead to exacerbation of corticosteroid-responsive illness. Patients on prolonged cortico-steroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

Cardiovascular Effects

The information below should be taken into consideration and caution should be exercised when VIOXX® is used in patients with a medical history of ischemic heart disease.

In VIGOR, a study in 8076 patients (mean age 58; VIOXX® n=4047, naproxen n=4029) with a median duration of exposure of 9 months, the risk of developing a serious cardiovascular thrombotic event was significantly higher in patients treated with VIOXX® 50 mg once daily (n=45) as compared to patients treated with naproxen 500 mg twice daily (n=19). In VIGOR, mortality due to cardiovascular thrombotic events (7 vs 6, VIOXX® vs naproxen, respectively) was similar between the treatment groups (see ACTION AND CLINICAL PHARMACOLOGY, Clinical Studies, Gastrointestinal Safety, Clinical Upper GI Outcomes, VIOXX® GI Clinical Outcomes Research (VIGOR) Study). In a placebo-controlled trials database derived from 2 studies with a total of 2142 elderly patients (mean age 75; VIOXX® n=1067, placebo n=1075) with a median duration of exposure of approximately 14 months, the number of patients with serious cardiovascular thrombotic events was 21 vs 35 for patients treated with VIOXX® 25 mg once daily versus placebo, respectively. In these same 2 placebo-controlled studies, mortality due to cardiovascular thrombotic events was 8 vs 3 for VIOXX® versus placebo, respectively. The significance of the cardiovascular findings from these 3 studies (VIGOR and 2 placebo-controlled studies) is unknown. Prospective studies specifically designed to compare the incidence of serious CV events in patients taking VIOXX® versus NSAID comparators or placebo have not been performed.

Because of its lack of platelet effects, VIOXX® is not a substitute for ASA for cardiovascular prophylaxis. Therefore, in patients taking VIOXX®, antiplatelet therapies should not be discontinued and should be considered in patients with an indication for cardiovascular prophylaxis (see ACTION AND CLINICAL PHARMACOLOGY, Clinical Studies, Special Studies, Platelet Function and PRECAUTIONS, Drug Interactions, ASA). Prospective, long-term studies on concomitant administration of VIOXX® and ASA evaluating cardiovascular outcomes have not been conducted.

Fluid Retention, Edema and Hypertension

Fluid retention, edema, and hypertension have been observed in some patients taking VIOXX®. Clinical trials with VIOXX® at daily doses of 12.5 and 25 mg in patients with osteoarthritis have shown effects on hypertension and edema similar to those observed

with comparator NSAIDs. In RA clinical trials, the incidence of hypertension was twice as high in patients receiving rofecoxib 25 mg daily, compared to patients treated with naproxen 1000 mg daily. Effects on blood pressure and fluid retention occur with an increased frequency with chronic use of VIOXX® at doses above 25 mg (see ADVERSE REACTIONS). VIOXX® should be used with caution, and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.

Renal Function

See ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Renal Insufficiency, WARNINGS, Advanced Renal Disease, and DOSAGE AND ADMINISTRATION.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal toxicity has also been seen in patients in whom renal prostaglandins have a compensatory role in the maintenance of renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate overt renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and angiotensin converting enzyme (ACE) inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. (see ADVERSE REACTIONS).

Caution should be used when initiating treatment with VIOXX® in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with VIOXX®. Caution is also recommended in patients with pre-existing kidney disease (see WARNINGS, Advanced Renal Disease).

Gastrointestinal System

There is no definitive evidence that the concomitant administration of histamine H_2-receptor antagonists and/or antacids will either prevent the occurrence of gastrointestinal side effects or allow the continuation of VIOXX® when and if these adverse reactions appear.

Genitourinary Tract

Some NSAIDs are known to cause persistent urinary symptoms (bladder pain, dysuria, urinary frequency), hematuria or cystitis. The onset of these symptoms may occur at any time after the initiation of therapy with an NSAID. Some cases have become severe on continued treatment. Should urinary symptoms occur, treatment with VIOXX® must be stopped immediately to obtain recovery. This should be done before any urological investigations or treatments are carried out.

Hepatic Function

Borderline elevations of one or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. These laboratory abnormalities may progress, may remain unchanged, or may be transient with continuing therapy. Rare cases of severe hepatic reactions, including jaundice and fatal fulminant hepatitis, liver necrosis and hepatic failure (some with fatal outcome) have been reported with NSAIDs. In controlled clinical trials of VIOXX®, the incidence of borderline elevations of liver tests at doses of 12.5 and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking rofecoxib (12.5 or 25 mg once a day) and 0.1% of patients taking placebo had notable elevations of ALT or AST.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, VIOXX® should be discontinued (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations, Hepatic Insufficiency).

Hematology

Anemia is sometimes seen in patients receiving VIOXX®. In placebo-controlled trials, there were no significant differences observed between VIOXX® and placebo in clinical reports of anemia. Patients on long-term treatment with VIOXX® should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. VIOXX® does not generally affect platelet counts, prothrombin time (PT), or partial thromboplastin time (PTT), and does not inhibit platelet aggregation at indicated dosages (see ACTION AND CLINICAL PHARMACOLOGY, Clinical Studies, Special Studies, Platelet Function).

Infections

VIOXX® may mask fever, which is a sign of infection. The physician should be aware of this when using VIOXX® in patients being treated for infection.

Ophthalmology

Blurred and/or diminished vision has been reported with the use of nonsteroidal anti-inflammatory drugs. If such symptoms develop, VIOXX® should be discontinued and an ophthalmologic examination performed; ophthalmologic examination should be carried out at periodic intervals in any patient receiving VIOXX® for an extended period of time.

Central Nervous System

Some patients may experience drowsiness, dizziness, vertigo, insomnia or depression with the use of nonsteroidal anti-inflammatory drugs. If patients experience these side effects, they should exercise caution in carrying out activities that require alertness.

Hypersensitivity Reactions

Patients with asthma may have ASA-sensitive asthma. The use of ASA in patients with ASA-sensitive asthma has been associated with severe bronchospasm which can be fatal. Since cross reactivity, including bronchospasm, between ASA and other nonsteroidal anti-inflammatory drugs has been reported in such ASA-sensitive patients, VIOXX® should not be administered to patients with this form of ASA sensitivity and should be used with caution in patients with pre-existing asthma.

Use in the Elderly

Of the total number of subjects in clinical studies of VIOXX®, 2886 subjects (33.6%) were 65 and over, 939 subjects (10.9%) were 75 and over, while 463 subjects (5.4%) were 80 and over. No overall differences in safety or effectiveness were observed between elderly and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients.

In one of these studies (a six-week, double-blind, placebo-controlled, randomized clinical trial), in 341 osteoarthritic patients $\geq$80 years of age, one-third of these patients were low-dose (less than or equal to 325 mg daily) ASA users. Patients treated with VIOXX® had an adverse experience profile generally similar to patients treated with placebo.

Drug Interactions

ACE Inhibitors: Reports suggest that NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors. In patients with mild-to-moderate hypertension, administration of 25 mg daily of VIOXX® with the ACE inhibitor benazepril, 10 to 40 mg for 4 weeks, was associated with an average increase in mean arterial pressure of about 3 mmHg compared to ACE inhibitor alone. This interaction should be given consideration in patients taking VIOXX® concomitantly with ACE inhibitors.

ASA: VIOXX® can be used with low-dose ASA. However, concomitant administration of low-dose ASA with VIOXX® may result in an increased rate of GI ulceration or other complications, compared to use of VIOXX® alone. At steady state, VIOXX® 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) ASA, as assessed by *ex vivo* platelet aggregation and serum thromboxane B_2 (TXB_2) generation in clotting blood (see ACTION AND CLINICAL PHARMACOLOGY, Clinical Studies, Special Studies, ASA and Use with Acetylsalicylic Acid). Because of its lack of platelet effects, VIOXX® is not a substitute for ASA for cardiovascular prophylaxis. Therefore, in patients taking VIOXX®, antiplatelet therapies should not be discontinued and should

be considered in patients with an indication for cardiovascular prophylaxis (see ACTION AND CLINICAL PHARMACOLOGY, Clinical Studies, Special Studies, Platelet Function and PRECAUTIONS, Cardiovascular Effects.) Prospective, long-term studies on concomitant administration of VIOXX® and ASA have not been conducted.

Cimetidine: Co-administration with high doses of cimetidine (800 mg twice daily) increased the C_{max} of rofecoxib by 21%, the $AUC_{0\text{-}120hr}$ by 23% and the $t_{1/2}$ by 15%. These changes are not clinically significant and no dose adjustment is necessary.

Digoxin: In a pharmacokinetic study in healthy volunteers, rofecoxib 75 mg once daily for 11 days did not alter the plasma concentration profile or renal elimination of digoxin after a single 0.5 mg oral dose. However, patients at high risk of digoxin toxicity, in whom renal prostaglandins may be important in maintaining renal function, should be monitored when rofecoxib and digoxin are administered concomitantly.

Diuretics: Clinical studies, as well as post-marketing observations, have shown that NSAIDs can reduce the natriuretic effect of furosemide and thiazides in some patients. This response has been attributed to inhibition of renal prostaglandin synthesis.

Ketoconazole: Ketoconazole 400 mg daily did not have any clinically important effect on the pharmacokinetics of rofecoxib.

Lithium: In post-marketing experience there have been reports of increases in plasma lithium levels.

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 $AUC_{0\text{-}24hr}$ 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 $AUC_{0\text{-}24hr}$ in patients receiving methotrexate 7.5 to 15 mg/week for rheumatoid arthritis. An equivalent magnitude of reduction in methotrexate renal clearance was observed. 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.

Warfarin: Prothrombin time (measured as International Normalized Ratio [INR]) increased in both single and multiple dose cross over studies in healthy individuals receiving both warfarin and rofecoxib. In a 21-day multiple-dose study in healthy individuals stabilized on warfarin (2 to 8.5 mg daily), administration of rofecoxib 25 mg once a day was associated with mean increases in INR of approximately 8% (range of INR on warfarin alone, 1.1 to 2.2; range of INR on warfarin plus rofecoxib, 1.2 to 2.4). Somewhat greater mean increases in INR of approximately 11% (range of maximum INR on warfarin alone, 1.5 to 2.7; range of maximum INR on warfarin plus rofecoxib, 1.6 to 4.4) were also seen in a single dose pharmacokinetic (PK) screening study using a 30 mg dose of warfarin and 50 mg of rofecoxib. In post-marketing experience there have been reports of increases in INR, some of which prompted reversal of anticoagulation, in patients taking VIOXX® at clinical doses concurrently with warfarin. Standard monitoring of INR values should be conducted when therapy with VIOXX® is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

Theophylline: VIOXX® 12.5, 25, and 50 mg administered once daily for 7 days increased plasma theophylline concentrations ($AUC_{(0-\infty)}$) by 38 to 60% 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.

Other Drug Interactions: Pharmacokinetic studies 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 CYP1A2 (e.g., amitriptyline, tacrine, zileuton and clozapine) in addition to rifampin and theophylline. No drug interaction data are available for VIOXX® and the co-administration of the following products: acetaminophen, alcohol, aminoglycosides, bone marrow depressants except methotrexate (see PRECAUTIONS, Drug Interactions, Methotrexate), butemide, cholestyramine, colchicine, cyclosporine, gold compounds, indapamide, insulin, nephrotoxic agents, nonsteroidal anti-inflammatory agents, potassium supplements, probenecid, valproic acid, zidovudine.

ADVERSE REACTIONS

Osteoarthritis (OA)

Approximately 3600 patients with osteoarthritis were treated with VIOXX® (rofecoxib); approximately 1400 patients received VIOXX® for 6 months or longer and approximately 800 patients for one year or longer. The following table of adverse experiences lists all adverse events, regardless of causality, occurring in at least 2% of patients receiving VIOXX® in nine controlled studies of 6-week to 6-month duration conducted in patients with OA at the therapeutically recommended doses (12.5 and 25 mg), which included a placebo and/or positive control group.

Clinical Adverse Experiences Occurring in ≥ 2.0% of Patients Treated with VIOXX®	VIOXX® 12.5 or 25 mg daily	Placebo	Ibuprofen 2400 mg daily	Diclofenac 150 mg daily
	(n = 2829)	(n = 783)	(n = 847)	(n = 498)
Body as a Whole/Site Unspecified				
Abdominal Pain	3.4	4.1	4.6	5.8
Asthenia/Fatigue	2.2	1.0	2.0	2.6
Dizziness	3.0	2.2	2.7	3.4
Influenza-Like Disease	2.9	3.1	1.5	3.2
Lower Extremity Edema	3.7	1.1	3.8	3.4
Upper Respiratory Infection	8.5	7.8	5.8	8.2
Cardiovascular System				
Hypertension	3.5	1.3	3	1.6
Digestive System				
Diarrhea	6.5	6.8	7.1	10.6
Dyspepsia	3.5	2.7	4.7	4.0
Epigastric Discomfort	3.8	2.8	9.2	5.4
Heartburn	4.2	3.6	5.2	4.6
Nausea	5.2	2.9	7.1	7.4
Eyes, Ears, Nose, and Throat				
Sinusitis	2.7	2	1.8	2.4
Musculoskeletal System				
Back Pain	2.5	1.9	1.4	2.8
Nervous System				
Headache	4.7	7.5	6.1	8
Respiratory System				
Bronchitis	2	0.8	1.4	3.2
Urogenital System				
Urinary Tract Infection	2.8	2.7	2.5	3.6

In the OA studies, the following spontaneous adverse events occurred in >0.1% to 1.9% of patients treated with VIOXX® regardless of causality:

Body as a Whole: abdominal distension, abdominal tenderness, abscess, chest pain, chills, contusion, cyst, diaphragmatic hernia, fever, fluid retention, flushing, fungal infection, infection, laceration, pain, pelvic pain, peripheral edema, post-operative pain, syncope, trauma, upper extremity edema, viral syndrome.

Cardiovascular System: angina pectoris, atrial fibrillation, bradycardia, hematoma, irregular heartbeat, palpitation, premature ventricular contraction, tachycardia, venous insufficiency.

Digestive System: acid reflux, aphthous stomatitis, constipation, dental caries, dental pain, digestive gas symptoms, dry mouth, duodenal disorder, dysgeusia, esophagitis, flatulence, gastric disorder, gastritis, gastroenteritis, hematochezia, hemorrhoids, infectious gastroenteritis, oral infection, oral lesion, oral ulcer, vomiting.

Eyes, Ears, Nose, and Throat: allergic rhinitis, blurred vision, cerumen impaction, conjunctivitis, dry throat, epistaxis, laryngitis, nasal congestion, nasal secretion, ophthalmic injection, otic pain, otitis, otitis media, pharyngitis, tinnitus, tonsillitis.

Immune System: allergy, insect bite reaction.

Metabolism and Nutrition: appetite change, hypercholesterolemia, weight gain.

Musculoskeletal System: ankle sprain, arm pain, arthralgia, back strain, bursitis, cartilage trauma, joint swelling, muscular cramp, muscular disorder, muscular weakness, musculoskeletal pain, musculoskeletal stiffness, myalgia, osteoarthritis, tendinitis, traumatic arthropathy, wrist fracture.

Nervous System: hypesthesia, insomnia, median nerve neuropathy, migraine, muscular spasm, paresthesia, sciatica, somnolence, vertigo.

Psychiatric Disorder: anxiety, depression, mental acuity decreased.

Respiratory System: asthma, cough, dyspnea, pneumonia, pulmonary congestion, respiratory infection.

Skin and Skin Appendages: abrasion, alopecia, atopic dermatitis, basal cell carcinoma, blister, cellulitis, contact dermatitis, herpes simplex, herpes zoster, nail unit disorder, perspiration, pruritus, rash, skin erythema, urticaria, xerosis.

Urogenital System: breast mass, cystitis, dysuria, menopausal symptoms, menstrual disorder, nocturia, urinary retention, vaginitis.

Other Serious Adverse Reactions Which Occur Rarely (<0.1%), Regardless of Causality: The following serious adverse events have occurred rarely in patients taking VIOXX®:

Cardiovascular: cerebrovascular accident, congestive heart failure, deep venous thrombosis, myocardial infarction, pulmonary embolism, transient ischemic attack, unstable angina.

Gastrointestinal: colitis, colonic malignant neoplasm, cholecystitis, duodenal ulcer, gastrointestinal bleeding, intestinal obstruction, pancreatitis.

Hemic and Lymphatic: lymphoma.

Urogenital: breast malignant neoplasm, prostatic malignant neoplasm, urolithiasis.

In 1-year controlled clinical trials and in extension studies for up to 86 weeks (approximately 800 patients treated with VIOXX® for one year or longer), the adverse experience profile was qualitatively similar to that observed in studies of shorter duration.

Rheumatoid Arthritis

Approximately 1100 patients were treated with VIOXX® in the rheumatoid arthritis efficacy studies. The adverse experience profile was generally similar to that reported in the osteoarthritis studies. In clinical studies, the following additional adverse

experiences occurred at an incidence of at least 2% in RA patients treated with VIOXX® 25 mg: pharyngitis, pruritus, and rash.

Analgesia, Including Primary Dysmenorrhea

Approximately one thousand patients were treated with VIOXX® in analgesia studies. All patients in post-dental surgery pain studies received only a single dose of study medication. Patients in primary dysmenorrhea studies may have taken up to 3 daily doses of VIOXX®, and those in the post-orthopedic surgery pain study were prescribed 5 daily doses of VIOXX®.

The adverse experience profile in the analgesia studies was generally similar to those reported in the osteoarthritis studies. The following additional adverse experience, which occurred at an incidence of at least 2% of patients treated with VIOXX®, was observed in the post-dental pain surgery studies: post-dental extraction alveolitis (dry socket).

In 110 patients treated with VIOXX® (average age approximately 65 years) in the post-orthopedic surgery pain study, the most commonly reported adverse experiences were constipation, fever, and nausea.

Clinical Studies in OA and RA with VIOXX® 50 mg (Twice the highest dose recommended for chronic use in OA)

In OA and RA clinical trials which contained VIOXX® 12.5 or 25 mg as well as VIOXX® 50 mg, VIOXX® 50 mg once a day was associated with a higher incidence of gastrointestinal symptoms (abdominal pain, epigastric pain, heartburn, nausea and vomiting), lower extremity edema, hypertension, serious* adverse experiences and discontinuations due to clinical adverse experiences compared to the recommended chronic doses of 12.5 and 25 mg (see PRECAUTIONS, Fluid Retention, Edema and Hypertension and ACTIONS AND CLINICAL PHARMA-COLOGY, Clinical Studies,

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* Adverse experience that resulted in death, permanent or substantial disability, hospitalization, congenital anomaly, or cancer, was immediately life threatening, was due to an overdose, or was thought by the investigator to require intervention to prevent one of the above outcomes.

Gastrointestinal Safety, Clinical Upper GI Outcomes, VIOXX® GI Clinical Outcomes Research (VIGOR) Study and DOSAGE AND ADMINISTRATION).

Post-Marketing Experience

The following adverse reactions have been reported in post-marketing experience:

Body as a Whole: dizziness, hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, angioedema, bronchospasm, pruritus, rash, urticaria, vasculitis.

Cardiovascular: congestive heart failure, hypertensive crisis, pulmonary edema.

Digestive: constipation, hepatic failure, hepatitis, jaundice, pancreatitis, peptic ulcers including perforation and bleeding (mainly in elderly patients), vomiting.

Hematologic: aplastic anemia, leukopenia, pancytopenia, thrombocytopenia.

Nervous System and Neuropsychiatric: anxiety, aseptic meningitis, confusion, decreased mental acuity, drowsiness, epilepsy aggravated, hallucinations, hypesthesia/ paresthesia.

Skin and Skin Appendages: alopecia, photosensitivity reactions, severe skin reactions, including Stevens-Johnson syndrome and toxic epidermal necrolysis.

Urogenital: hyperkalemia, interstitial nephritis, renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy (see PRECAUTIONS, Renal Function).

Laboratory Test Findings

INR: increases in INR during concomitant therapy with warfarin (see PRECAUTIONS, Drug Interactions, Warfarin).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No overdoses of VIOXX® (rofecoxib) were reported during clinical trials.

In clinical studies, administration of single doses of VIOXX® at up to 1000 mg and multiple doses up to 250 mg/day for 14 days did not result in significant toxicity.

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

Rofecoxib is not dialyzable by hemodialysis; it is not known whether rofecoxib is dialyzable by peritoneal dialysis.

DOSAGE AND ADMINISTRATION

VIOXX® (rofecoxib) is administered orally.

Osteoarthritis

The recommended starting dose is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily. The maximum recommended daily dose is 25 mg. Patients should be maintained on the lowest individual effective dose (see ACTION AND CLINICAL PHARMACOLOGY, Clinical Studies, Osteoarthritis).

Rheumatoid Arthritis

The recommended dose is 25 mg once daily. The maximum recommended daily dose is 25 mg. A 50 mg dose once daily of VIOXX® was also studied; however, no significant additional efficacy was seen compared to the 25 mg dose. Patients should be maintained on the lowest individual effective dose (see ACTION AND CLINICAL PHARMACOLOGY, Clinical Studies, Rheumatoid Arthritis).

Relief of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended initial dose is 50 mg once daily. Subsequent doses should be 25 to 50 mg once daily. The maximum recommended daily dose is 50 mg. VIOXX® was studied in the management of acute pain for up to 5 days. Chronic use of 50 mg daily is not recommended (see ACTION AND CLINICAL PHARMACOLOGY, Clinical studies, Analgesia, Including Primary Dysmenorrhea).

No dosage adjustment is necessary for elderly patients, for patients with mild-to-moderate renal insufficiency (creatinine clearance 30 to 80 mL/min) or for patients with mild hepatic insufficiency (Child-Pugh score 5-6). In patients with moderate hepatic insufficiency (Child-Pugh score 7-9), the lowest possible dose is recommended. In chronic use, the maximum recommended daily dose is 12.5 mg There are no clinical data in patients with severe hepatic insufficiency (Child-Pugh score >9) (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Special Populations).

VIOXX® may be taken with or without food.

Oral Suspension

VIOXX® oral suspension 12.5 mg/5 mL or 25 mg/5 mL may be substituted for VIOXX® tablets 12.5 or 25 mg, respectively, in any of the above indications.

PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

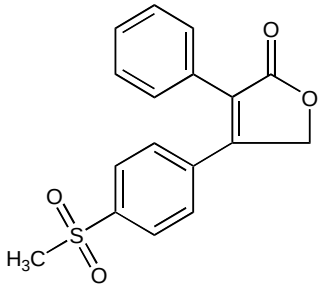
Proper name: Rofecoxib

Chemical name: 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5*H)*-furanone

Molecular formula: $C_{17}H_{14}O_4S$

Molecular weight: 314.36

Structural formula:



Description: Rofecoxib is a white to off-white to light yellow powder. Rofecoxib is sparingly soluble in acetone, slightly soluble in methanol and isopropyl acetate, very slightly soluble in ethanol, practically insoluble in octanol, and insoluble in water.

II. COMPOSITION

Each tablet of VIOXX® (rofecoxib) for oral administration contains either 12.5, 25 or 50 mg of rofecoxib and the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide. The 50 mg tablets also contain red ferric oxide.

Each 5 mL of the oral suspension contains either 12.5 or 25 mg of rofecoxib and the following inactive ingredients: citric acid (monohydrate), purified water, sodium citrate (dihydrate), sorbitol solution, strawberry flavor, and xanthan gum. Added as preservatives are sodium methylparaben 0.13% and sodium propylparaben 0.02%.

III. STABILITY AND STORAGE RECOMMENDATIONS

VIOXX® Tablets:

Store at 25˚C, excursions permitted to 15˚C-30˚C (room temperature).

VIOXX® Oral Suspension:

Store at 25˚C, excursions permitted to 15˚C-30˚C (room temperature). Protect from freezing. Shake well before using.

AVAILABILITY OF DOSAGE FORMS

VIOXX® 12.5 mg tablets, are cream/off-white, round, shallow cup tablets engraved MRK 74 on one side and VIOXX on the other. Available in blister packages of 10 and 30, and in bottles of 30, 90, 100 and 1000 tablets.

VIOXX® 25 mg tablets, are yellow, round tablets engraved MRK 110 on one side and VIOXX on the other. Available in blister packages of 10 and 30, and in bottles of 30, 90, 100 and 1000 tablets.

VIOXX® 50 mg tablets, are orange, round tablets engraved MRK 114 on one side and VIOXX on the other. Available in blister packages of 10 and 30, and in bottles of 30, 90, and 100 tablets.

VIOXX® oral suspension, 12.5 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking. Available in bottles containing 150 mL (12.5 mg/5 mL).

VIOXX® oral suspension, 25 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking. Available in bottles containing 150 mL (25 mg/5 mL).

INFORMATION FOR THE PATIENT

for Osteoarthritis, Rheumatoid Arthritis and Pain

VIOXX® (rofecoxib) Tablets and Oral Suspension

Please read this leaflet carefully before you start to take your medicine, even if you have just refilled your prescription. Some of the information in the previous leaflet may have changed.

What is VIOXX®?

VIOXX® is a nonsteroidal anti-inflammatory drug (NSAID) which reduces the joint swelling, redness and pain of arthritis. Your body produces chemicals called prostaglandins. Some of these prostaglandins help line the stomach with a protective layer. In arthritis, other prostaglandins cause pain and swelling. VIOXX® reduces the type that causes pain and swelling. At prescribed doses, VIOXX® does not affect the type that maintains the protective layer of the stomach, and reduces the chances of bleeding.

This medicine does not cure arthritis, but promotes suppression of the inflammation and tissue damaging effects resulting from this inflammation. VIOXX® will help you only as long as you continue to take it.

VIOXX® is available as a tablet or an oral liquid.

Why has my doctor prescribed VIOXX®?

Your doctor has prescribed VIOXX® for:

- treatment of osteoarthritis
- treatment of rheumatoid arthritis
- relief of pain
- treatment of menstrual pain

What is osteoarthritis?

Osteoarthritis is a joint disease caused by age-related “wear and tear” on bones and joints. It results from the gradual breakdown of the cartilage that cushions the ends of bones, resulting in pain, inflammation, tenderness, stiffness, and physical disability.

What is rheumatoid arthritis?

Rheumatoid arthritis is a chronic disease that causes pain, stiffness, swelling and loss of function in the joints and inflammation in other body organs.

What else can I do to help manage my arthritis?

Talk to your doctor about:

- Exercise
- Controlling your weight
- Hot and cold treatments
- Using support devices

BEFORE TAKING THIS MEDICATION TELL YOUR DOCTOR AND PHARMACIST IF YOU:

- or a family member are allergic to or have had a reaction to the active or inactive ingredients contained in VIOXX®, or to other anti-inflammatory drugs (such as acetylsalicylic acid [ASA], diclofenac, diflunisal, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, mefenamic acid, naproxen, piroxicam, sulindac, tiaprofenic acid, tolmetin, nabumetone or tenoxicam) manifesting itself by increased sinusitis, hives, the initiating or worsening of asthma or anaphylaxis (sudden collapse);
- or a family member have had asthma, nasal polyps, chronic sinusitis or chronic urticaria (hives);
- have a history of stomach upset, ulcers, liver or kidney diseases;
- have blood or urine abnormalities;
- have a history of angina, heart attack or a blocked artery in your heart;
- have high blood pressure or heart failure;
- have fluid retention like swelling of the legs;

- have diabetes;
- are on any special diet, such as a low-sodium or low-sugar diet;
- are pregnant or intend to become pregnant while taking this medication;
- are breast-feeding or intend to breast-feed while taking this medication;
- are taking any other medication (either prescription or non-prescription) such as NSAIDs, theophylline (a medicine used to treat asthma), warfarin (a blood thinner), rifampin (an antibiotic), angiotensin converting enzyme (ACE) inhibitors (medicines used for high blood pressure and heart failure), or lithium (a medicine used to treat a certain type of depression).

WHILE TAKING THIS MEDICATION

- tell any other doctor, dentist or pharmacist that you consult or see, that you are taking this medication;
- some NSAIDs may cause drowsiness or fatigue in some people taking them. Do not drive or participate in activities that require alertness if you are drowsy, dizzy or lightheaded after taking this medication;
- check with your doctor if you are not getting any relief of your arthritis or if any problems develop;
- report any untoward reactions to your doctor. This is very important as it will aid in the early detection and prevention of potential complications;
- stomach problems may be more likely to occur if you drink alcoholic beverages. Therefore, do not drink alcoholic beverages while taking this medication;
- check with your doctor immediately if you experience unexpected weakness while taking this medication, or if you vomit any blood or have dark or bloody stools;
- some people may become more sensitive to sunlight than they are normally. Exposure to sunlight or sunlamps, even for brief periods of time, may cause sunburn, blisters on the skin, skin rash, redness, itching or discoloration, or vision changes. If you have a reaction from the sun, check with your doctor;
- check with your doctor immediately if chills, fever, muscle aches or pains, or other flu-like symptoms occur, especially if they occur shortly before or together with a skin rash. Very rarely, these effects may be the first signs of a serious reaction to this medication;

- **YOUR REGULAR MEDICAL CHECKUPS ARE ESSENTIAL.**

SIDE EFFECTS OF THIS MEDICATION

Along with its beneficial effects, VIOXX® may occasionally cause some undesirable reactions, especially when used for a long time or in large doses.

Elderly, frail or debilitated patients often seem to experience more frequent or more severe side effects. Although these side effects are not common, when they do occur they may require medical attention.

CHECK WITH YOUR DOCTOR IMMEDIATELY IF ANY OF THE FOLLOWING ARE NOTED:

- Serious stomach problems such as ulcer or bleeding symptoms (for instance, stomach burning or black tarry stools, which are signs of possible stomach bleeding);
- shortness of breath, wheezing, any trouble in breathing or tightness in the chest;
- chest pain, palpitations;
- allergic reactions (which may be serious enough to require immediate medical attention) including swelling of the face, lips, tongue, and/or throat which may cause difficulty in breathing or swallowing, hives, rash, and itching;
- severe skin reactions, skin reactions caused by sunlight;
- vomiting or persistent indigestion, nausea, stomach pain, colitis or diarrhea;
- yellow discoloration of the skin or eyes;
- any change in the amount of or colour of your urine (dark red or brown);
- any pain or difficulty experienced while urinating;
- swelling of the feet or lower legs;
- unexplained weight gain;
- malaise, fatigue, drowsiness, loss of appetite;
- blurred vision or any visual disturbance;
- anxiety, mental confusion, difficulty concentrating, depression, insomnia, dizziness, lightheadedness, hallucinations, tingling sensation, headache, vertigo (false sensation of movement or spinning);
- unusual headache with stiff neck (aseptic meningitis);

- hearing problems;
- hair loss

Heart attacks and similar serious events have been reported in patients taking VIOXX®.

Additionally, the following have been reported: heart failure; serious kidney problems, increased levels of potassium in the blood, decreased levels of sodium in the blood, fluid in the lungs, low blood cell counts, pancreatitis, serious liver problems, severe increase in blood pressure, menstrual disorder, ringing in the ears, constipation, dry mouth, worsening of epilepsy.

Other side effects not listed above may also occur in some patients. If you notice any other effects that you may consider important, check with your doctor or pharmacist without delay.

How should I take VIOXX®?

VIOXX® should be taken once a day.
You may take VIOXX® with or without food.

For treatment of osteoarthritis:

- The recommended starting dose is 12.5 mg once a day.
- Your doctor may increase the dose to 25 mg once a day.
- The maximum recommended dose is 25 mg once a day.

For treatment of rheumatoid arthritis:

- The recommended dose is 25 mg once a day.
- The maximum recommended daily dose is 25 mg.

For the relief of acute pain and the treatment of menstrual pain:

- On the first day, the recommended initial dose is 50 mg once a day.
- On the second day and after that, the dose should be 25 or 50 mg once a day as prescribed by your doctor.

- The maximum recommended dose is 50 mg once a day.
- VIOXX® was studied in the management of acute pain for up to 5 days.

VIOXX® can be taken with low-dose ASA (less than or equal to 325 mg daily) when indicated by a doctor. If you are currently taking low-dose ASA for prevention of heart attack or stroke, you should not discontinue without consulting your doctor because VIOXX® is not a substitute for ASA for prevention of heart attack or stroke.

Your doctor will decide what dose of VIOXX® you should take and how long you should take it. If you have moderate liver disease, you should not take more than 12.5 mg a day in long-term use.

What should I do if I miss a dose?

Try to take VIOXX® as prescribed. However, if you miss a dose, do not take an extra dose. Just resume your usual schedule the following day.

What should I do in case of an overdose?

If you take more than the prescribed dosage, contact your doctor immediately.

How should I store VIOXX®?

Tablets: Store at room temperature (15˚C-30˚C).

Oral Suspension: Store at room temperature (15˚C-30˚C). Protect from freezing. Shake well before using.

VIOXX® IS NOT RECOMMENDED FOR PATIENTS UNDER 18 YEARS OF AGE SINCE SAFETY AND EFFECTIVENESS HAVE NOT BEEN ESTABLISHED.

DO NOT TAKE VIOXX® DURING PREGNANCY UNLESS SPECIFICALLY PRESCRIBED BY A DOCTOR.

DO NOT KEEP OUTDATED MEDICINE OR MEDICINE NO LONGER NEEDED.

KEEP OUT OF THE REACH OF CHILDREN.

THIS MEDICINE HAS BEEN PRESCRIBED FOR YOUR MEDICAL PROBLEM. DO NOT GIVE IT TO ANYONE ELSE.

VIOXX® tablets contain the following inactive ingredients: croscarmellose sodium, hydroxypropyl cellulose, lactose, magnesium stearate, microcrystalline cellulose, and yellow ferric oxide. The 50 mg tablets also contain red ferric oxide.

VIOXX® oral suspension contains the following inactive ingredients: citric acid (monohydrate), purified water, sodium citrate (dihydrate), sorbitol solution, strawberry flavor, and xanthan gum. Added as preservatives are sodium methylparaben 0.13% and sodium propylparaben 0.02%.

PHARMACOLOGY

Mechanism of Action (see ACTION AND CLINICAL PHARMACOLOGY)
The anti-inflammatory effects of VIOXX® (rofecoxib) were demonstrated in standard animal models used to evaluate cyclooxygenase inhibitors. Administered orally, VIOXX® reversed swelling and hyperalgesia caused by intraplantar carrageenan injection in rats. Further, VIOXX® inhibited swelling associated with adjuvant-induced arthritis in rats. In these studies, the anti-inflammatory effect of VIOXX® was similar to indomethacin.

In *ex vivo* human whole blood assays, serum thromboxane B_2 (TXB_2) concentration and lipopolysaccharide (LPS) induced prostaglandin E_2 (PGE_2) generation were used to measure COX-1 and COX-2 activity, respectively. In subjects receiving doses of VIOXX® 12.5 and 25 mg/day or clinically recommended doses of several nonselective COX inhibitors, including nabumetone, etodolac, meloxicam, ibuprofen, diclofenac, and naproxen, LPS-induced PGE_2 generation (COX-2) was inhibited by approximately 50% or more. However, at these doses of VIOXX® and even with multiple doses up to 375 mg daily (15- to 30-fold the clinical dose for osteoarthritis) and single doses up to 1000 mg (40- to 80-fold the clinical dose for osteoarthritis), there was no dose-dependent inhibition of COX-1 compared with placebo. In contrast, nonselective COX inhibitors at the clinically recommended doses significantly inhibited COX-1 (nabumetone 73%; etodolac 41%; diclofenac 50-60%; meloxicam 53%; ibuprofen 89%; and naproxen 95%).

In addition, urinary excretion of 11-dehydro TXB_2 was used as a measure of *in vivo* COX-1 activity. VIOXX® 12.5, 25, and 50 mg daily did not inhibit COX-1 activity based on the absence of any significant reduction in the urinary excretion of 11-dehydro TXB_2 compared with placebo. In contrast, three nonselective COX inhibitors, i.e., meloxicam, diclofenac, and indomethacin substantially decreased the urinary excretion of 11-dehydro TXB_2 compared with placebo ($p<0.01$ for each NSAID).

The influence on gastroprotective COX-1 activity was also assessed in a clinical study

where prostaglandin synthesis was measured in gastric biopsy samples from subjects administered either VIOXX® 25 mg daily, naproxen 500 mg twice daily, or placebo. VIOXX® did not inhibit gastric prostaglandin synthesis. In contrast, naproxen inhibited gastric prostaglandin synthesis by >70% compared with placebo. These data, together with the whole blood and urinary prostanoid biochemical assays, support the COX-2 selectivity of rofecoxib.

TOXICOLOGY

Acute Toxicity

No mortality occurred following a single oral or intraperitoneal administration of rofecoxib at doses up to 2000 mg/kg, the maximum dose tested (oral aLD50 >2000 mg/kg) in female mice (6000 mg/m^2) and rats, (11,800 mg/m^2). This dose is >26 times the recommended daily adult human dose based on systemic exposure.

Chronic Toxicity

The toxicity potential of rofecoxib was evaluated in a series of repeated-dose oral toxicity studies up to 53 weeks in dogs and rats. In each species, the principal treatment-related changes were associated with renal and intestinal toxicity. Both the renal and intestinal lesions were shown to occur at dosages above the intended clinical dose of 25 mg daily.

In dogs administered rofecoxib orally at dosages of 50 mg/kg/day (~14 times the recommended daily adult human dose based on systemic exposure) for 14 weeks, toxicity was characterized by intestinal ulceration and focal renal papillary necrosis. No renal or intestinal toxicity was seen in dogs administered 30 mg/kg/day for 53 weeks.

In rats, rofecoxib administered orally at dosages of 10 mg/kg/day (~8 times the recommended daily adult human dose based on systemic exposure) or higher following 27 weeks of administration produced renal effects. Renal changes were predominately characterized by renal tubular basophilia noted in a dose dependent manner. Renal

papillary necrosis was noted in 1 animal each at dosages of 100 and 300 mg/kg/day.

Due to species-specific enterohepatic recirculation of rofecoxib, intestinal ulceration, principally jejunal ulcers, often associated with physical signs, clinical pathologic changes consistent with blood loss, peritonitis, and death, was observed in rats administered oral doses of rofecoxib $\geq$2 mg/kg/day (~1.4 times the recommended daily adult human dose based on systemic exposure). There were no gastric ulcers directly related to treatment with rofecoxib. The no-observed-effect level (NOEL) for intestinal ulceration was 1.0 mg/kg/day following 53 weeks of daily oral administration to rats.

Carcinogenicity

Rofecoxib was not carcinogenic in mice given oral doses up to 30 mg/kg (male) and 60 mg/kg (female) (approximately 5- and 2-fold the human exposure at 25 and 50 mg daily based on $AUC_{0\text{-}24hr}$) and in male and female rats given oral doses up to 8 mg/kg (approximately 6- and 2-fold the human exposure at 25 and 50 mg daily based on $AUC_{0\text{-}24hr}$) for two years.

Mutagenesis

Rofecoxib was not mutagenic in an Ames test or in a V-79 mammalian cell mutagenesis assay, nor clastogenic in a chromosome aberration assay in Chinese hamster ovary (CHO) cells, in an *in vitro* and an *in vivo* alkaline elution assay, or in an *in vivo* chromosomal aberration test in mouse bone marrow.

Reproduction and Teratology

Rofecoxib did not impair male fertility in rats at oral doses up to 100 mg/kg (approximately 20- and 7-fold human exposure at 25 and 50 mg daily based on the $AUC_{0\text{-}24hr}$) and rofecoxib had no effect on fertility in female rats at doses up to 30 mg/kg (approximately 19- and 7-fold human exposure at 25 and 50 mg daily based on $AUC_{0\text{-}24hr}$).

Rofecoxib was not teratogenic in rats at doses up to 50 mg/kg/day (approximately 28- and 10-fold human exposure at 25 and 50 mg daily based on $AUC_{0\text{-}24hr}$). There was a slight, non-statistically significant increase in the overall incidence of vertebral malformations only in the rabbit at doses of 50 mg/kg/day (approximately 1- or < 1 -fold human exposure at 25 and 50 mg daily based on $AUC_{0\text{-}24hr}$).

There are no studies in pregnant women. VIOXX® (rofecoxib) should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Rofecoxib produced peri-implantation and post-implantation losses and reduced embryo/fetal survival in rats and rabbits at oral doses $\geq$ 10 and $\geq$ 75 mg/kg/day, respectively (approximately 9- and 3-fold [rats] and 2- and < 1-fold [rabbits] human exposure based on the $AUC_{0\text{-}24hr}$ at 25 and 50 mg daily). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function. There was an increase in the incidence of postnatal pup mortality in rats at $\geq$ 5 mg/kg/day (approximately 5- and 2-fold human exposure at 25 and 50 mg daily based on $AUC_{0\text{-}24hr}$). In studies in pregnant rats administered single doses of rofecoxib, there was a treatment-related decrease in the diameter of the ductus arteriosus at all doses used (3-300 mg/kg: 3 mg/kg is approximately 2- and < 1 -fold human exposure at 25 or 50 mg daily based on $AUC_{0\text{-}24hr}$). As with other drugs known to inhibit prostaglandin synthesis, use of VIOXX® during the third trimester of pregnancy should be avoided.

Rofecoxib produced no evidence of significantly delayed labor or parturition in females at doses of 15 mg/kg in rats (approximately 10- and 3-fold human exposure as measured by the $AUC_{0\text{-}24hr}$ at 25 and 50 mg). The effects of VIOXX® on labor and delivery in pregnant women are unknown.

Rofecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. There was an increase in pup mortality and a decrease in pup body weight following exposure of pups to milk from dams administered VI0XX® during lactation. The dose tested represents an approximate 18- and 6-fold human exposure at 25 and 50

mg based on $AUC_{0\text{-}24hr}$. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VIOXX®, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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