VIOXX®
(rofecoxib tablets and oral suspension)

WARNING: RISK OF SERIOUS CARDIOVASCULAR AND GASTROINTESTINAL EVENTS

Cardiovascular Thrombotic Events

- **Nonsteroidal anti-inflammatory drugs (NSAIDs) cause an increased risk of serious cardiovascular thrombotic events, including myocardial infarction and stroke, which can be fatal. This risk may occur early in treatment and may increase with duration of use (*see WARNINGS)*.**

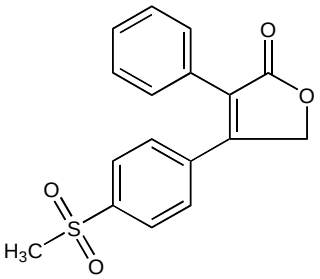
- **VIOXX is contraindicated in the setting of coronary artery bypass graft (CABG) surgery *(see CONTRAINDICATIONS, WARNINGS)*.**

Gastrointestinal Bleeding, Ulceration, and Perforation

- **NSAIDs cause an increased risk of serious gastrointestinal (GI) adverse events including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients and patients with a prior history of peptic ulcer disease and/or GI bleeding are at greater risk for serious GI events. *(see WARNINGS)*.**

DESCRIPTION

VIOXX® (rofecoxib) is a nonsteroidal anti-inflammatory drug (NSAID). The chemical name is 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(*5H*)-furanone. The molecular weight is 314.36. The empirical formula for rofecoxib is $C_{17}H_{14}O_4S$, and it has the following chemical structure:



Rofecoxib is a white to off-white to light yellow powder. It 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.

Each tablet of VIOXX for oral administration contains either 12.5 mg, 25 mg, 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), sodium citrate (dihydrate), sorbitol solution, strawberry flavor, xanthan gum, and purified water. Added as preservatives are sodium methylparaben 0.13% and sodium propylparaben 0.02%.

CLINICAL PHARMACOLOGY

Mechanism of Action

Rofecoxib has analgesic, anti-inflammatory, and antipyretic properties.

The mechanism of action of VIOXX, like that of other NSAIDs, is not completely understood, but involves inhibition of cyclooxygenase (COX-1 and COX-2). At therapeutic concentrations in humans, VIOXX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

Rofecoxib is a potent inhibitor of prostaglandin synthesis *in vitro*. Rofecoxib concentrations reached during therapy have produced *in vivo* effects. Prostaglandins sensitize afferent nerves and potentiate the action of bradykinin in inducing pain in animal models. Prostaglandins are mediators of inflammation. Because rofecoxib is an inhibitor of prostaglandin synthesis, its mode of action may be due to a decrease of prostaglandins in peripheral tissues.

Studies to elucidate the mechanism of action of VIOXX in the acute treatment of migraine have not been conducted.

Pharmacokinetics

Absorption

The mean oral bioavailability of VIOXX at therapeutically recommended doses of 12.5, 25, and 50 mg is approximately 93%. The area under the curve (AUC) and peak plasma level (C_{max}) following a single 25-mg dose were 3286 (±843) ng•hr/mL and 207 (±111) 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. The plasma concentration-time profile exhibited multiple peaks. The median time to maximal concentration (T_{max}), as assessed in nine pharmacokinetic studies, is 2 to 3 hours. Individual T_{max} values in these studies ranged between 2 to 9 hours. This may not reflect rate of absorption as T_{max} may occur as a secondary peak in some individuals. With multiple dosing, steady-state conditions are reached by Day 4. The $AUC_{0\text{-}24hr}$ and C_{max} at steady state after multiple doses of 25 mg rofecoxib was 4018 (±1140) ng•hr/mL and 321 (±104) ng/mL, respectively, in healthy adults. The accumulation factor based on geometric means was 1.67. The $AUC_{0\text{-}24hr}$ and C_{max} at steady state after multiple doses of 25 mg rofecoxib was 6934 (±2158) ng•hr/mL and 519 (±163) ng/mL, respectively, in adult RA patients (N=12, mean body weight 62 kg).

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 (see *PRECAUTIONS; Drug Interactions*).

Distribution

Rofecoxib is approximately 87% bound to human plasma protein over the range of concentrations of 0.05 to 25 mcg/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 has been shown to cross the placenta in rats and rabbits, and the blood-brain barrier in rats.

Elimination

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 plasma clearance after 12.5- and 25-mg doses was approximately 141 and 120 mL/min, respectively. Higher plasma clearance was observed at doses below the therapeutic range, suggesting the presence of a saturable route of metabolism (i.e., non-linear elimination). The effective half-life (based on steady-state levels) was approximately 17 hours.

Special Populations

Sex

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.

Pediatric

The steady state pharmacokinetics of rofecoxib was evaluated in patients ≥ 2 years to ≤ 17 years of age who weigh more than 10 kg with pauciarticular and polyarticular course Juvenile Rheumatoid Arthritis (JRA). The apparent clearance after oral administration of rofecoxib in patients ≥ 12 years to ≤ 17 years of age was similar to that of healthy adults and higher than that of adult RA patients. The apparent clearance after oral administration of rofecoxib in patients ≥ 2 years to ≤ 11 years of age was less than that of adults and increased with age. The apparent oral clearance of rofecoxib increases with body weight (and body surface area). (See Table 1.)

Table 1
Rofecoxib Apparent Oral Clearance (CL/F, mean ± SD) in JRA Patients* and Adults.

	JRA patients			Adults	
Group	2- to 5-year-old (N=21)	6- to 11-year-old (N=13)	12- to 17-year-old (N=11)	Healthy Age range: 20-48 (N=26)	RA Patients Age range: 31-64 (N=12)
Body Weight (kg) (mean ± SD)	17 ± 2	29 ± 6	57 ± 13	77 ± 13	62 ± 11
CL/F (mL/min)	37 ± 15	52 ± 13	87 ± 21	96 ± 30	65 ± 20

* Pauciarticular and Polyarticular Course JRA

A dose of 0.6 mg/kg to a maximum of 25 mg once daily in patients ≥ 2 years to ≤ 11 years of age and body weight 10 kg or above and a dose of 25 mg once daily in patients ≥ 12 years to ≤ 17 years of age would yield an AUC slightly higher than that of the 25-mg tablet once daily in healthy adults (AUC Geometric Mean Ratio, 1.12) and slightly lower than that in adult RA patients (AUC GMR, 0.77).

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 Impairment

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 mean rofecoxib plasma concentrations were higher (mean AUC: 55%; mean C_{max}: 53%) relative to healthy subjects. Since patients with hepatic insufficiency are prone to fluid retention and hemodynamic compromise, the maximum recommended chronic dose of VIOXX for patients with moderate hepatic insufficiency is 12.5 mg daily. (*see WARNINGS; Hepatotoxicity, DOSAGE AND ADMINISTRATION; Hepatic Insufficiency)*. Patients with severe hepatic insufficiency have not been studied. Therefore, Vioxx should not be used in patients with severe hepatic insufficiency.

Renal Impairment

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. *(see WARNINGS; Renal Toxicity and Hyperkalemia)*.

Drug Interaction Studies

Aspirin

When NSAIDs were administered with aspirin, the protein binding of NSAIDs were reduced, although the clearance of free NSAID was not altered. The clinical significance of this interaction is not known. See Table 6 for clinically significant drug interactions of NSAIDs with aspirin. *(See PRECAUTIONS; 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 $AUC_{0\text{-}24hr}$ 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. 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) (see *PRECAUTIONS; Drug Interactions*)

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% (see *PRECAUTIONS; Drug Interactions*).

General

In human studies the potential for rofecoxib to inhibit or induce CYP 3A4 activity was investigated in studies using the intravenous erythromycin breath test and the oral midazolam test. No significant difference in erythromycin demethylation was observed with rofecoxib (75 mg daily) compared to placebo, indicating no induction of hepatic CYP 3A4. A 30% reduction of the AUC of midazolam was observed with rofecoxib (25 mg daily). This reduction is most likely due to increased first pass metabolism through induction of intestinal CYP 3A4 by rofecoxib. *In vitro* studies in rat hepatocytes also suggest that rofecoxib might be a mild inducer for CYP 3A4.

Drug interaction studies with the recommended doses of rofecoxib have identified potentially significant interactions with rifampin, theophylline, and warfarin. Patients receiving these agents with VIOXX should be appropriately monitored. Drug interaction studies do not support the potential for clinically important interactions between antacids or cimetidine with rofecoxib. Similar to experience with other nonsteroidal anti-inflammatory drugs (NSAIDs), studies with rofecoxib suggest the potential for interaction with ACE inhibitors. The effects of rofecoxib on the pharmacokinetics and/or pharmacodynamics of ketoconazole, prednisone/prednisolone, oral contraceptives, and digoxin have been studied *in vivo* and clinically important interactions have not been found.

CLINICAL STUDIES

Adults

Osteoarthritis (OA)

VIOXX has demonstrated significant reduction in joint pain compared to placebo. VIOXX was evaluated for the treatment of the signs and symptoms of OA of the knee and hip in placebo- and active-controlled clinical trials of 6 to 86 weeks duration that enrolled approximately 3900 patients. In patients with OA, treatment with VIOXX 12.5 mg and 25 mg once daily resulted in improvement in patient and physician global assessments and in the WOMAC (Western Ontario and McMaster Universities) osteoarthritis questionnaire, including pain, stiffness, and functional measures of OA. In six studies of pain accompanying OA flare, VIOXX provided a significant reduction in pain at the first determination (after one week in one study, after two weeks in the remaining five studies); this continued for the duration of the studies. In all OA clinical studies, once daily treatment in the morning with VIOXX 12.5 and 25 mg was associated with a significant reduction in joint stiffness upon first awakening in the morning. At doses of 12.5 and 25 mg, the effectiveness of VIOXX was shown to be comparable to ibuprofen 800 mg TID and diclofenac 50 mg TID for treatment of the signs and symptoms of OA. The ibuprofen studies were 6-week studies; the diclofenac studies were 12-month studies in which patients could receive additional arthritis medication during the last 6 months.

Rheumatoid Arthritis (RA)

VIOXX has demonstrated significant reduction of 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 2,000 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. A 50-mg dose once daily of VIOXX was also studied; however, no additional efficacy was seen compared to the 25-mg dose.

Analgesia, including Dysmenorrhea

In acute analgesic models of post-operative dental pain, post-orthopedic surgical pain, and primary dysmenorrhea, VIOXX relieved pain that was rated by patients as moderate to severe. The analgesic effect (including onset of action) of a single 50-mg dose of VIOXX was generally similar to 550 mg of naproxen sodium or 400 mg of ibuprofen. In single-dose post-operative dental pain studies, the onset of analgesia with a single 50-mg dose of VIOXX occurred within 45 minutes. In a multiple-dose study of post-orthopedic surgical pain in which patients received VIOXX or placebo for up to 5 days, 50 mg of VIOXX once daily was effective in reducing pain. In this study, patients on VIOXX consumed a significantly smaller amount of additional analgesic medication than patients treated with placebo (1.5 versus 2.5 doses per day of additional analgesic medication for VIOXX and placebo, respectively).

Migraine with or without aura

The efficacy of VIOXX in the acute treatment of migraine headaches was demonstrated in two double-blind, placebo-controlled, outpatient trials. Doses of 25 and 50 mg were compared to placebo in the treatment of one migraine attack. A second dose of VIOXX was not allowed in either trial. In these controlled short-term studies, patients were predominantly female (88%) and Caucasian (84%), with a mean age of 40 years (range 18 to 78). Patients were instructed to treat a moderate to severe headache. Headache relief, defined as a reduction in headache severity from moderate or severe pain to mild or no pain, was assessed up to 2 hours after dosing. Associated symptoms such as nausea, photophobia, and phonophobia were also assessed. Maintenance of relief was assessed for up to 24 hours postdose. Other medication, with the exception of NSAIDs (including COX-2 inhibitors) or combination medications that contained NSAIDs, was permitted from 2 hours after the dose of study medication. The frequency and time to use of additional medications were also recorded.

In both placebo-controlled trials, the percentage of patients achieving headache relief 2 hours after treatment was significantly greater among patients receiving VIOXX at all doses compared to those who

received placebo (Table 2). There were no statistically significant differences between the 25- and the 50-mg dose groups in either trial.

Table 2
Percentage of Patients with Headache Relief (Mild or No Headache)
2 hours Following Treatment

Trial	VIOXX 25 mg	VIOXX 50 mg	Placebo
1	54%* (n=176)	57%* (n=187)	34% (n=175)
2	60%* (n=187)	62%* (n=188)	30% (n=187)

*p<0.0001 vs. placebo

Note that, in general, comparisons of results obtained in different clinical studies conducted under different conditions by different investigators with different samples of patients are ordinarily unreliable for purposes of quantitative comparison.

The estimated probability of achieving initial headache relief within 2 hours following treatment is depicted in Figure 1.

Figure 1
Estimated Probability of Achieving Initial Headache Relief within 2 Hours

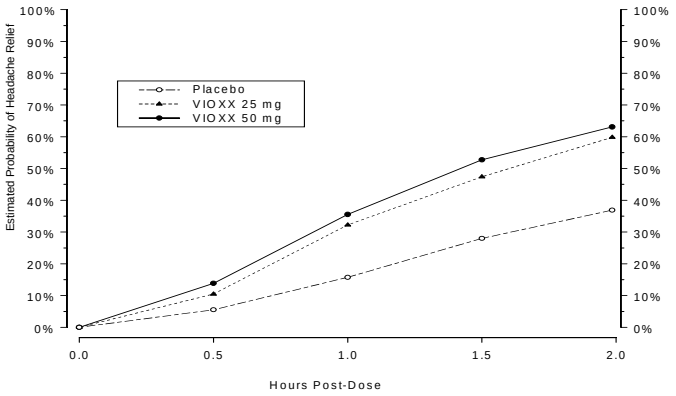
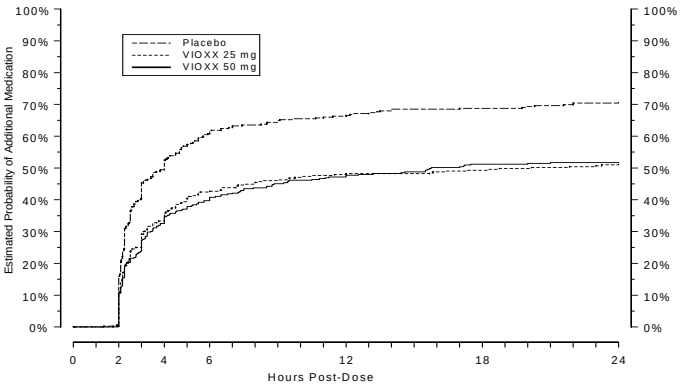


Figure 1 shows the Kaplan-Meier plot of the probability over time of obtaining headache relief (no or mild pain) following treatment with VIOXX or placebo. The plot is based on pooled data from the 2 placebo-controlled, outpatient trials in adults providing evidence of efficacy. Patients taking additional medication or not achieving headache relief prior to 2 hours were censored at 2 hours.

There was a decreased incidence of migraine-associated nausea, photophobia and phonophobia in VIOXX treated patients compared to placebo. The estimated probability of taking other medication for migraine over the 24 hours following initial dose of study treatment is summarized in Figure 2.

Figure 2
Estimated Probability of Patients Taking Additional Medication for Migraines
over the 24 Hours Following the Initial Dose of Study Treatment



This Kaplan-Meier plot is based on pooled data obtained in 2 placebo-controlled outpatient trials. Patients not using additional medications were censored at 24 hours. The plot includes both patients who had headache relief at 2 hours and those who had no response to the initial dose. Additional medication was not allowed within 2 hours postdose.

VIOXX was effective regardless of presence of aura, gender, race, age, presence of menses or dysmenorrhea. Similarly, the concomitant use of common migraine prophylactic drugs (e.g., beta-blockers, calcium channel blockers, tricyclic antidepressants) or oral contraceptives did not affect efficacy. VIOXX was also effective whether or not there was a history of prior response to NSAIDs.

Special Studies

The following special studies were conducted to evaluate the comparative safety of VIOXX.

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 and RA) 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 aspirin or other antiplatelet drugs. Patients with a recent history of myocardial infarction or stroke and patients deemed to require low-dose aspirin 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 3).

Table 3
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 ≤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 10 1/2 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 4). This finding was largely due to a difference in the incidence of myocardial infarction between the groups. (See Table 5.) *(see WARNINGS; Cardiovascular Thrombotic Events.)* 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 4
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 remaining 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 5
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 WARNINGS, *Cardiovascular Thrombotic Events*.

Upper Endoscopy in Patients with Osteoarthritis and Rheumatoid Arthritis

The VIGOR study described above compared clinically relevant outcomes. Several studies summarized below have utilized scheduled endoscopic evaluations to assess the occurrence of asymptomatic ulcers in individual patients taking VIOXX or a comparative agent. The results of outcomes studies, such as VIGOR, are more clinically relevant than the results of endoscopy studies (see CLINICAL STUDIES, *Special Studies, VIGOR*).

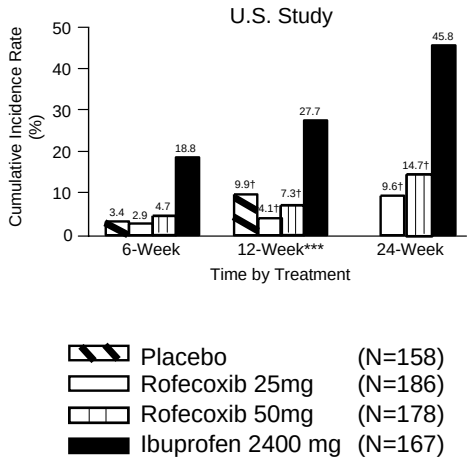
Two identical (U.S. and Multinational) endoscopy studies in a total of 1516 patients were conducted to compare the percentage of patients who developed endoscopically detectable gastroduodenal ulcers with VIOXX 25 mg daily or 50 mg daily, ibuprofen 2400 mg daily, or placebo. Entry criteria for these studies permitted enrollment of patients with active *Helicobacter pylori* infection, baseline gastroduodenal erosions, prior history of an upper gastrointestinal perforation, ulcer, or bleed (PUB), and/or age ≥65 years. However, patients receiving aspirin (including low-dose aspirin for cardiovascular prophylaxis) were not enrolled in these studies. Patients who were 50 years of age and older with osteoarthritis and who had no ulcers at baseline were evaluated by endoscopy after weeks 6, 12, and 24 of treatment. The placebo-treatment group was discontinued at week 16 by design.

Treatment with VIOXX 25 mg daily or 50 mg daily was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. See Figures 3 and 4 for the results of these studies.

Figure 3

COMPARISON TO IBUPROFEN

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

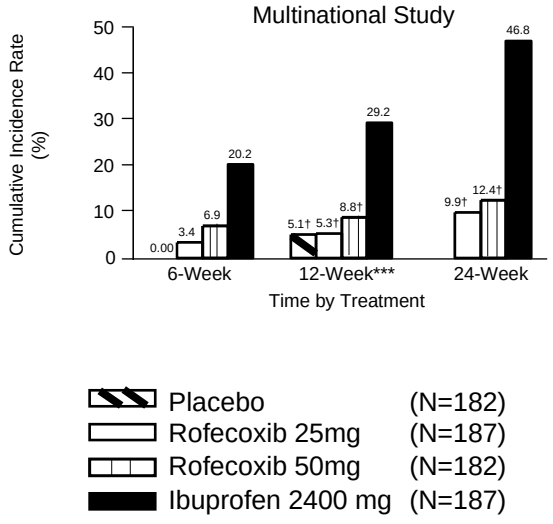


† p < 0.001 versus ibuprofen 2400 mg
** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were consistent.
*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

Figure 4

COMPARISON TO IBUPROFEN

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



† p < 0.001 versus ibuprofen 2400 mg
** Results of analyses using a ≥ 5mm gastroduodenal ulcer endpoint were consistent.
*** The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

In a similarly designed 12-week endoscopy study in RA patients treated with VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA and RA) or naproxen 1000 mg daily (common therapeutic dose), treatment with VIOXX was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with naproxen.

A similarly designed 12-week endoscopy study was conducted in OA patients treated with low-dose enteric coated aspirin 81 mg daily, low-dose enteric coated aspirin 81 mg plus VIOXX 25 mg daily, ibuprofen 2400 mg daily, or placebo. There was no difference in the cumulative incidence of endoscopic gastroduodenal ulcers in patients taking low-dose aspirin plus VIOXX 25 mg as compared to those taking ibuprofen 2400 mg daily alone. Patients taking low-dose aspirin plus ibuprofen were not studied. *(see PRECAUTIONS; Drug Interactions,)*

Serious clinically significant upper GI bleeding has been observed in patients receiving VIOXX in controlled trials, albeit infrequently *(see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation)*.

Assessment of Fecal Occult Blood Loss in Healthy Subjects

Occult fecal blood loss associated with VIOXX 25 mg daily, VIOXX 50 mg daily, ibuprofen 2400 mg per day, and placebo was evaluated 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, the increase in the amount of fecal blood loss was not statistically significant compared with placebo-treated subjects. In contrast, ibuprofen 2400 mg per day produced a statistically significant increase in fecal blood loss as compared with placebo-treated subjects and VIOXX-treated subjects. The clinical relevance of this finding is unknown.

Platelets

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. There was no inhibition of *ex vivo* arachidonic acid- or collagen-induced platelet aggregation with 12.5, 25, and 50 mg of VIOXX.

Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. (*see WARNINGS; Cardiovascular Thrombotic Events*).

Pediatric Patients

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis (JRA)

In a 12-week, double-blind active-controlled, non-inferiority study, 310 patients, 2 years to 17 years of age with pauciarticular or polyarticular course JRA, received the following treatments: lower-dose VIOXX 0.3 mg/kg (to a maximum of 12.5 mg) once daily in patients $\geq$ 2 years to $\leq$ 11 years of age or VIOXX 12.5 mg once daily in patients $\geq$ 12 years to $\leq$ 17 years of age; higher-dose VIOXX 0.6 mg/kg (to a maximum of 25 mg) once daily in patients $\geq$ 2 years to $\leq$ 11 years of age or VIOXX 25 mg once daily in patients $\geq$ 12 years to $\leq$ 17 years of age; NSAID comparator targeted to an effective dose in patients $\geq$ 2 years to $\leq$ 17 years of age. The response rates were based upon the JRA Definition of Improvement $\geq$ 30% (JRA DOI 30) criterion, which is a composite of clinical, laboratory, and functional measures of JRA. The JRA DOI 30 response rates were 55% in both the VIOXX 0.6 mg/kg (to a maximum of 25 mg) and NSAID comparator treatment groups achieving the non-inferiority criterion. A single non-inferiority trial is not sufficient to support a conclusion of equivalence.

In a 52-week open-label extension to the 12-week study, 160 patients received VIOXX 0.6 mg/kg to a maximum of 25 mg once daily (patients $\geq$ 2 years to $\leq$ 11 years of age) or 25 mg once daily (patients $\geq$ 12 years to $\leq$ 17 years of age) and 67 patients $\geq$ 2 years to $\leq$ 17 years of age received NSAID comparator targeted to an effective dose. There were no unexpected safety findings.

INDICATIONS AND USAGE

VIOXX is indicated:

- For relief of the signs and symptoms of osteoarthritis.
- For relief of the signs and symptoms of rheumatoid arthritis in adults.

- For relief of the signs and symptoms of pauciarticular or polyarticular course Juvenile Rheumatoid Arthritis (JRA) in patients 2 years and older and who weigh 10 kg (22 lbs) or more.
- For the management of acute pain in adults.
- For the treatment of primary dysmenorrhea.
- For the acute treatment of migraine attacks with or without aura in adults.

The safety and effectiveness of VIOXX have not been established for cluster headache, which is present in an older, predominantly male, population.

CONTRAINDICATIONS

VIOXX is contraindicated in the following patients:

- Known hypersensitivity (e.g., anaphylactic reactions and serious skin reactions) to rofecoxib or any components of the drug product. *(see WARNINGS; Anaphylactic Reactions* and WARNINGS, *Serious Skin Reactions*).

- History of asthma, urticaria, or other allergic-type reactions after taking aspirin or other NSAIDs. Severe, sometimes fatal, anaphylactic reactions to NSAIDs have been reported in such patients (*see WARNINGS; Anaphylactic Reactions, Exacerbation of Asthma Related to Aspirin Sensitivity*).

- *In the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS; Cardiovascular Thrombotic Events)*.

WARNINGS

Cardiovascular Thrombotic Events

Clinical trials of several COX-2 selective and nonselective NSAIDs of up to three years duration have shown an increased risk of serious cardiovascular (CV) thrombotic events, including myocardial infarction (MI) and stroke, which can be fatal. Based on available data, it is unclear that the risk for CV thrombotic events is similar for all NSAIDs. The relative increase in serious CV thrombotic events over baseline conferred by NSAID use appears to be similar in those with and without known CV disease or risk factors for CV disease. However, patients with known CV disease or risk factors had a higher absolute incidence of excess serious CV thrombotic events, due to their increased baseline rate. Some observational studies found that this increased risk of serious CV thrombotic events began as early as the first weeks of treatment. The increase in CV thrombotic risk has been observed most consistently at higher doses.

To minimize the potential risk for an adverse CV event in NSAID-treated patients, use the lowest effective dose for the shortest duration possible. Physicians and patients should remain alert for the development of such events, throughout the entire treatment course, even in the absence of previous CV symptoms. Patients should be informed about the symptoms of serious CV events and the steps to take if they occur.

There is no consistent evidence that concurrent use of aspirin mitigates the increased risk of serious CV thrombotic events associated with NSAID use. The concurrent use of aspirin and an NSAID, such as rofecoxib, increases the risk of serious gastrointestinal (GI) events. (see WARNINGS; *Gastrointestinal Bleeding, Ulceration, and Perforation*).

Status Post Coronary Artery Bypass Graft (CABG) Surgery

Two large, controlled clinical trials of a COX-2 selective NSAID for the treatment of pain in the first 10–14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. NSAIDs are contraindicated in the setting of CABG *(see CONTRAINDICATIONS)*.

Post-MI Patients

Observational studies conducted in the Danish National Registry have demonstrated that patients treated with NSAIDs in the post-MI period were at increased risk of reinfarction, CV-related death, and all-cause mortality beginning in the first week of treatment. In this same cohort, the incidence of death in the

first year post-MI was 20 per 100 person years in NSAID-treated patients compared to 12 per 100 person years in non-NSAID exposed patients. Although the absolute rate of death declined somewhat after the first year post-MI, the increased relative risk of death in NSAID users persisted over at least the next four years of follow-up.

Avoid the use of VIOXX in patients with a recent MI unless the benefits are expected to outweigh the risk of recurrent CV thrombotic events. If VIOXX is used in patients with a recent MI, monitor patients for signs of cardiac ischemia.

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 CLINICAL STUDIES, *Special Studies*, *VIGOR*, *Other Safety Findings: Cardiovascular Safety*.) In a placebo-controlled 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 aspirin 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.

Gastrointestinal Bleeding, Ulceration, and Perforation

NSAIDs, including rofecoxib, cause serious gastrointestinal (GI) adverse events including inflammation, bleeding, ulceration, and perforation of the esophagus, stomach, small intestine, or large intestine, which can be fatal. These serious adverse events can occur at any time, with or without warning symptoms, in patients treated with NSAIDs. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. Upper GI ulcers, gross bleeding, or perforation caused by NSAIDs occurred in approximately 1% of patients treated for 3-6 months, and in about 2%-4% of patients treated for one year. However, even short-term NSAID therapy is not without risk.

Risk Factors for GI Bleeding, Ulceration, and Perforation

Patients with a prior history of peptic ulcer disease and/or GI bleeding who used NSAIDs had a greater than 10-fold increased risk for developing a GI bleed compared to patients without these risk factors. Other factors that increase the risk for GI bleeding in patients treated with NSAIDs include longer duration of NSAID therapy; concomitant use of oral corticosteroids, aspirin, anticoagulants, or selective serotonin reuptake inhibitors (SSRIs); smoking; use of alcohol; older age; and poor general health status. Most postmarketing reports of fatal GI events occurred in elderly or debilitated patients. Additionally, patients with advanced liver disease and/or coagulopathy are at increased risk for GI bleeding.

Strategies to Minimize the GI Risks in NSAID-treated patients:

- Use the lowest effective dosage for the shortest possible duration.
- Avoid administration of more than one NSAID at a time.
- Avoid use in patients at higher risk unless benefits are expected to outweigh the increased risk of bleeding. For such patients, as well as those with active GI bleeding, consider alternate therapies other than NSAIDs.
- Remain alert for signs and symptoms of GI ulceration and bleeding during NSAID therapy.
- If a serious GI adverse event is suspected, promptly initiate evaluation and treatment, and discontinue VIOXX until a serious GI adverse event is ruled out.
- In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, monitor patients more closely for evidence of GI bleeding (see PRECAUTIONS, *Drug Interactions*).

Although the risk of GI toxicity is not completely eliminated with VIOXX, the results of the VIOXX GI 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 CLINICAL STUDIES, *Special Studies, VIGOR*.)

Hepatotoxicity

Elevations of ALT or AST (three or more times the upper limit of normal [ULN]) have been reported in approximately 1% of NSAID-treated patients in clinical trials. In addition, rare, sometimes fatal, cases of severe hepatic injury, including fulminant hepatitis, liver necrosis, and hepatic failure have been reported.

Elevations of ALT or AST (less than three times ULN) may occur in up to 15% of patients treated with NSAIDs, including rofecoxib.

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.

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, diarrhea, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), discontinue VIOXX immediately, and perform a clinical evaluation of the patient.

Hypertension

NSAIDs, including VIOXX, can lead to new onset of hypertension or worsening of pre-existing hypertension, either of which may contribute to the increased incidence of CV events. Patients taking angiotensin converting enzyme (ACE) inhibitors, thiazide diuretics, or loop diuretics may have impaired response to these therapies when taking NSAIDs. (See PRECAUTIONS, *Drug Interactions*.)

In clinical trials of VIOXX at daily doses of 25 mg in patients with rheumatoid arthritis the incidence of hypertension was twice as high in patients treated with VIOXX as compared to patients treated with naproxen 1000 mg daily.

Monitor blood pressure (BP) during the initiation of NSAID treatment and throughout the course of therapy.

Heart Failure and Edema

The Coxib and traditional NSAID Trialists' Collaboration meta-analysis of randomized controlled trials demonstrated an approximately two-fold increase in hospitalizations for heart failure in COX-2 selective-treated patients and nonselective NSAID-treated patients compared to placebo-treated patients. In a Danish National Registry study of patients with heart failure, NSAID use increased the risk of MI, hospitalization for heart failure, and death.

Additionally, fluid retention and edema have been observed in some patients treated with NSAIDs. Use of rofecoxib may blunt the CV effects of several therapeutic agents used to treat these medical conditions (e.g., diuretics, ACE inhibitors, or angiotensin receptor blockers [ARBs]). *(see PRECAUTIONS; Drug Interactions)*.

Avoid the use of VIOXX in patients with severe heart failure unless the benefits are expected to outweigh the risk of worsening heart failure. If VIOXX is used in patients with severe heart failure, monitor patients for signs of worsening heart failure.

Renal Toxicity and Hyperkalemia

Renal Toxicity

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 an NSAID 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, dehydration, hypovolemia, heart failure, liver dysfunction, those taking diuretics and ACE inhibitors or ARBs, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state.

No information is available from controlled clinical studies regarding the use of VIOXX in patients with advanced renal disease. The renal effects of VIOXX may hasten the progression of renal dysfunction in patients with pre-existing renal disease.

Correct volume status in dehydrated or hypovolemic patients prior to initiating VIOXX. Monitor renal function in patients with renal or hepatic impairment, heart failure, dehydration, or hypovolemia during use of VIOXX *(see PRECAUTIONS; Drug Interactions*). Avoid the use of VIOXX in patients with advanced renal disease unless the benefits are expected to outweigh the risk of worsening renal function. If VIOXX is used in patients with advanced renal disease, monitor patients for signs of worsening renal function.

Hyperkalemia

Increases in serum potassium concentration, including hyperkalemia, have been reported with use of NSAIDs, even in some patients without renal impairment. In patients with normal renal function, these effects have been attributed to a hyporeninemic-hypoaldosteronism state.

Anaphylactic Reactions

Rofecoxib has been associated with anaphylactic reactions in patients with and without known hypersensitivity to rofecoxib and in patients with aspirin-sensitive asthma. *(see CONTRAINDICATIONS, WARNINGS; Exacerbation of Asthma Related to Aspirin Sensitivity.)*

Seek emergency help if an anaphylactic reaction occurs.

Exacerbation of Asthma Related to Aspirin Sensitivity

A subpopulation of patients with asthma may have aspirin-sensitive asthma which may include chronic rhinosinusitis complicated by nasal polyps; severe, potentially fatal bronchospasm; and/or intolerance to aspirin and other NSAIDs. Because cross-reactivity between aspirin and other NSAIDs has been reported in such aspirin-sensitive patients, VIOXX is contraindicated in patients with this form of aspirin sensitivity (*see CONTRAINDICATIONS)*. When VIOXX is used in patients with preexisting asthma (without known aspirin sensitivity), monitor patients for changes in the signs and symptoms of asthma.

Serious Skin Reactions

NSAIDs, including rofecoxib, can cause serious skin adverse reactions such as exfoliative dermatitis, Stevens-Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN), which can be fatal. These serious events may occur without warning. Inform patients about the signs and symptoms of serious skin reactions, and to discontinue the use of VIOXX at the first appearance of skin rash or any other sign of hypersensitivity. VIOXX is contraindicated in patients with previous serious skin reactions to NSAIDs. *(see CONTRAINDICATIONS).*

Premature Closure of the Fetal Ductus Arteriosus

Rofecoxib may cause premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including VIOXX, in pregnant women starting at 30 weeks of gestation (third trimester) *(see PRECAUTIONS; Pregnancy)*.

Hematologic Toxicity

Anemia has occurred in NSAID-treated patients. This may be due to occult or gross blood loss, fluid retention, or an incompletely described effect on erythropoiesis. If a patient treated with VIOXX has any signs or symptoms of anemia, monitor hemoglobin or hematocrit.

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 CLINICAL PHARMACOLOGY; CLINICAL STUDIES, Special Studies, Platelets)*.

NSAIDs, including VIOXX, may increase the risk of bleeding events. Co-morbid conditions such as coagulation disorders, or concomitant use of warfarin, other anticoagulants, antiplatelet agents (e.g., aspirin), serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) may increase this risk. Monitor these patients for signs of bleeding. *(see PRECAUTIONS; Drug Interactions).*

PRECAUTIONS

General

VIOXX 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 corticosteroid therapy should have their therapy tapered slowly if a decision is made to discontinue corticosteroids.

Information for Patients

Advise the patient to read the FDA-approved patient labeling (Medication Guide) that accompanies each prescription dispensed. Inform patients, families, or their caregivers of the following information before initiating therapy with VIOXX and periodically during the course of ongoing therapy.

Cardiovascular Thrombotic Events

Advise patients to be alert for the symptoms of cardiovascular thrombotic events, including chest pain, shortness of breath, weakness, or slurring of speech, and to report any of these symptoms to their health care provider immediately *(see WARNINGS; Cardiovascular Thrombotic Events*).

Gastrointestinal Bleeding, Ulceration, and Perforation

Advise patients to report symptoms of ulcerations and bleeding, including epigastric pain, dyspepsia, melena, and hematemesis to their health care provider. In the setting of concomitant use of low-dose aspirin for cardiac prophylaxis, inform patients of the increased risk for and the signs and symptoms of GI bleeding *(see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation)*.

Hepatotoxicity

Inform patients of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, diarrhea, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, instruct patients to stop VIOXX and seek immediate medical therapy. *(See WARNINGS; Hepatotoxicity.*)

Heart Failure and Edema

Advise patients to be alert for the symptoms of congestive heart failure including shortness of breath, unexplained weight gain, or edema and to contact their healthcare provider if such symptoms occur *(see WARNINGS; Heart Failure and Edema).*

Anaphylactic Reactions

Inform patients of the signs of an anaphylactic reaction (e.g., difficulty breathing, swelling of the face or throat). Instruct patients to seek immediate emergency help if these occur (see CONTRAINDICATIONS and WARNINGS, *Anaphylactic Reactions. (see CONTRAINDICATIONS, WARNINGS; Anaphylactic Reactions)*

Serious Skin Reactions

Advise patients to stop VIOXX immediately if they develop any type of rash and to contact their healthcare provider as soon as possible *(see WARNINGS; Serious Skin Reactions*).

Female Fertility

Advise females of reproductive potential who desire pregnancy that NSAIDs, including VIOXX, may be associated with a reversible delay in ovulation. *(see PRECAUTIONS; Carcinogenesis, Mutagenesis, Impairment of Fertility)*.

Fetal Toxicity

Inform pregnant women to avoid use of VIOXX and other NSAIDs starting at 30 weeks gestation because of the risk of the premature closing of the fetal ductus arteriosus *(see WARNINGS; Premature Closure of Fetal Ductus Arteriosus, PRECAUTIONS; Pregnancy)*.

Avoid Concomitant Use of NSAIDs

Inform patients that the concomitant use of VIOXX with other NSAIDs or salicylates (e.g., diflunisal, salsalate) is not recommended due to the increased risk of gastrointestinal toxicity, and little or no increase in efficacy *(see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation, PRECAUTIONS; Drug Interactions)*. Alert patients that NSAIDs may be present in "over the counter" medications for treatment of colds, fever, or insomnia.

Use of NSAIDs and Low-Dose Aspirin

Inform patients that VIOXX is not a substitute for aspirin for cardiovascular prophylaxis because of its lack of effect on platelets. Therefore, in patients taking VIOXX, antiplatelet therapies should not be discontinued and should be considered in patients with an indication for cardiovascular prophylaxis.

Masking of Inflammation and Fever

The pharmacological activity of VIOXX in reducing inflammation, and possibly fever, may diminish the utility of these diagnostic signs in detecting infectious complications of presumed noninfectious, painful conditions.

Laboratory Monitoring

Because serious GI bleeding, hepatotoxicity, and renal injury can occur without warning symptoms or signs, consider monitoring patients on long-term NSAID treatment with a CBC and a chemistry profile periodically (see WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation; Hepatotoxicity; and Renal Toxicity and Hyperkalemia)

Drug Interactions

See Table 6 for clinically significant drug interactions with rofecoxib.

Table 6: Clinically Significant Drug Interactions with Rofecoxib

Drugs That Interfere with Hemostasis	
Clinical Impact:	• Rofecoxib and anticoagulants such as warfarin have a synergistic effect on bleeding. The concomitant use of rofecoxib and anticoagulants have an increased risk of serious bleeding compared to the use of either drug alone. • In single and multiple dose studies in healthy subjects receiving both warfarin and rofecoxib, prothrombin time (measured as INR) was increased by approximately 8% to 11%. In post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin. • Serotonin release by platelets plays an important role in hemostasis. Case-control and cohort epidemiological studies showed that concomitant use of drugs that interfere with serotonin reuptake and an NSAID may potentiate the risk of bleeding more than an NSAID alone.
Intervention:	• Monitor patients with concomitant use of VIOXX with anticoagulants (e.g., warfarin), antiplatelet agents (e.g., aspirin), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) for signs of bleeding *(see WARNINGS; Hematologic Toxicity*).
Aspirin	
Clinical Impact:	Controlled clinical studies showed that the concomitant use of NSAIDs and analgesic doses of aspirin does not produce any greater therapeutic effect than the use of NSAIDs alone. In a clinical study, the concomitant use of an NSAID and aspirin was associated with a significantly increased incidence of

	GI adverse reactions as compared to use of the NSAID alone. *(See WARNINGS; Gastrointestinal Bleeding, Ulceration, and Perforation*). Concomitant administration of low-dose aspirin with VIOXX may result in an increased rate of GI ulceration or other complications, compared to use of VIOXX alone. In a 12-week endoscopy study conducted in OA patients there was no difference in the cumulative incidence of endoscopic gastroduodenal ulcers in patients taking low-dose (81 mg) enteric coated aspirin plus VIOXX 25 mg daily, as compared to those taking ibuprofen 2400 mg daily alone. Patients taking low-dose aspirin plus ibuprofen were not studied. (See CLINICAL STUDIES, *Special Studies, Upper Endoscopy in Patients with Osteoarthritis and Rheumatoid Arthritis*.) At steady state, VIOXX 50 mg once daily had no effect on the anti-platelet activity of low-dose (81 mg once daily) aspirin, as assessed by *ex vivo* platelet aggregation and serum TXB2 generation in clotting blood. Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. Prospective, long-term studies on concomitant administration of VIOXX and aspirin have not been conducted.
Intervention:	• Concomitant use of VIOXX and analgesic doses of aspirin is not generally recommended because of the increased risk of bleeding (see WARNINGS, *Hematologic Toxicity*). • In patients taking VIOXX, antiplatelet therapies should not be discontinued and should be considered in patients with an indication for cardiovascular prophylaxis. (See CLINICAL STUDIES, Special Studies, Platelets and WARNINGS, Cardiovascular Thrombotic Events.) VIOXX is not a substitute for low dose aspirin for cardiovascular protection.
ACE Inhibitors, Angiotensin Receptor Blockers, and Beta-Blockers	
Clinical Impact:	• NSAIDs may diminish the antihypertensive effect of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or beta-blockers (including propranolol). • In patients who are elderly, volume-depleted (including those on diuretic therapy), or have renal impairment, co-administration of an NSAID with ACE inhibitors or ARBs may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible.
Intervention:	• During concomitant use of VIOXX and ACE-inhibitors, ARBs, or beta-blockers, monitor blood pressure to ensure that the desired blood pressure is obtained. • During concomitant use of VIOXX and ACE-inhibitors or ARBs in patients who are elderly, volume-depleted, or have impaired renal function, monitor for signs of worsening renal function (see WARNINGS, *Renal Toxicity and Hyperkalemia*). • When these drugs are administered concomitantly, patients should be adequately hydrated. Assess renal function at the beginning of the concomitant treatment and periodically thereafter.
Diuretics	
Clinical Impact:	Clinical studies, as well as post-marketing observations, showed that NSAIDs reduced the natriuretic effect of loop diuretics (e.g., furosemide) and thiazide diuretics in some patients. This effect has been attributed to the NSAID inhibition of renal prostaglandin synthesis.
Intervention:	During concomitant use of VIOXX with diuretics, observe patients for signs of worsening renal function, in addition to assuring diuretic efficacy including antihypertensive effects (see WARNINGS, *Renal Toxicity and Hyperkalemia*).
Digoxin	
Clinical Impact:	The concomitant use of rofecoxib with digoxin has been reported to increase

	the serum concentration and prolong the half-life of digoxin.
Intervention:	During concomitant use of VIOXX and digoxin, monitor serum digoxin levels.
Lithium	
Clinical Impact:	NSAIDs have produced elevations in plasma lithium levels and reductions in renal lithium clearance. The mean minimum lithium concentration increased 15%, and the renal clearance decreased by approximately 20%. This effect has been attributed to NSAID inhibition of renal prostaglandin synthesis. In post-marketing experience there have been reports of increases in plasma lithium levels when VIOXX and lithium were administered concurrently.
Intervention:	During concomitant use of VIOXX and lithium, monitor patients for signs of lithium toxicity.
Methotrexate	
Clinical Impact:	Concomitant use of NSAIDs and methotrexate may increase the risk for methotrexate toxicity (e.g., neutropenia, thrombocytopenia, renal dysfunction).
Intervention:	During concomitant use of VIOXX and methotrexate, monitor patients for methotrexate toxicity.
Cyclosporine	
Clinical Impact:	Concomitant use of VIOXX and cyclosporine may increase cyclosporine's nephrotoxicity.
Intervention:	During concomitant use of VIOXX and cyclosporine, monitor patients for signs of worsening renal function.
NSAIDs and Salicylates	
Clinical Impact:	Concomitant use of rofecoxib with other NSAIDs or salicylates (e.g., diflunisal, salsalate) increases the risk of GI toxicity, with little or no increase in efficacy (see WARNINGS, *Gastrointestinal Bleeding, Ulceration, and Perforation*).
Intervention:	The concomitant use of rofecoxib with other NSAIDs or salicylates is not recommended.
Pemetrexed	
Clinical Impact:	Concomitant use of VIOXX and pemetrexed may increase the risk of pemetrexed-associated myelosuppression, renal, and GI toxicity (see the pemetrexed prescribing information).
Intervention:	During concomitant use of VIOXX and pemetrexed, in patients with renal impairment whose creatinine clearance ranges from 45 to 79 mL/min, monitor for myelosuppression, renal and GI toxicity. NSAIDs with short elimination half-lives (e.g., diclofenac, indomethacin) should be avoided for a period of two days before, the day of, and two days following administration of pemetrexed. In the absence of data regarding potential interaction between pemetrexed and NSAIDs with longer half-lives (e.g., meloxicam, nabumetone), patients taking these NSAIDs should interrupt dosing for at least five days before, the day of, and two days following pemetrexed administration.
Rifampin	
Clinical Impact:	Co-administration of VIOXX with rifampin 600 mg daily, a potent inducer of hepatic metabolism, produced an approximate 50% decrease in rofecoxib plasma concentrations.
Intervention:	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 such as rifampin.
Theophylline	
Clinical Impact:	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.
Intervention:	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).

Cimetidine: Co-administration with high doses of cimetidine [800 mg twice daily] has no significant effect on the pharmacokinetics of rofecoxib. The small changes in pharmacokinetics are not clinically significant and no dose adjustment is necessary [See *Clinical Pharmacology*].

Furosemide: 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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

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_{0-24}) 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_{0-24}) 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.

Impairment of Fertility

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_{0-24}) 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_{0-24}).

Pregnancy

Pregnancy Category C prior to 30 weeks gestation; Category D starting at 30 weeks gestation.

Use of NSAIDs, including VIOXX, during the third trimester of pregnancy increases the risk of premature closure of the fetal ductus arteriosus. Avoid use of NSAIDs, including VIOXX, in pregnant women starting at 30 weeks of gestation (third trimester).

There are no adequate and well-controlled studies of VIOXX in pregnant women. Data from observational studies regarding potential embryofetal risks of NSAID use in women in the first or second trimesters of pregnancy are inconclusive. In the general U.S. population, all clinically recognized pregnancies, regardless of drug exposure, have a background rate of 2-4% for major malformations, and

15-20% for pregnancy loss. 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_{0-24}). 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_{0-24}). Based on animal data, prostaglandins have been shown to have an important role in endometrial vascular permeability, blastocyst implantation, and decidualization. In animal studies, administration of prostaglandin synthesis inhibitors such as rofecoxib, resulted in increased pre- and post-implantation loss.

Rofecoxib produced peri-implantation and post-implantation losses and reduced embryo/fetal survival in rats and rabbits at oral doses ≥10 and ≥75 mg/kg/day, respectively (approximately 9- and 3-fold [rats] and 2- and <1-fold [rabbits] human exposure based on the AUC_{0-24} 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 ≥5 mg/kg/day (approximately 5- and 2-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). 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_{0-24}). As with other drugs known to inhibit prostaglandin synthesis, use of VIOXX during the third trimester of pregnancy should be avoided.

Labor or delivery

There are no studies on the effects of VIOXX during labor or delivery. In animal studies, NSAIDS, including rofecoxib, inhibit prostaglandin synthesis, cause delayed parturition, and increase the incidence of stillbirth. Rofecoxib produced no evidence of significantly delayed labor or parturition in females at doses 15 mg/kg in rats (approximately 10- and 3-fold human exposure as measured by the AUC_{0-24} at 25 and 50 mg). The effects of VIOXX on labor and delivery in pregnant women are unknown.

Nursing mothers

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 VIOXX during lactation. The dose tested represents an approximate 18- and 6-fold human exposure at 25 and 50 mg based on AUC_{0-24}. 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. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for VIOXX and any potential adverse effects on the breastfed infant from VIOXX or from the underlying maternal condition.

Infertility

Females

Based on the mechanism of action, the use of prostaglandin-mediated NSAIDs, including VIOXX, may delay or prevent rupture of ovarian follicles, which has been associated with reversible infertility in some women. Published animal studies have shown that administration of prostaglandin synthesis inhibitors has the potential to disrupt prostaglandin-mediated follicular rupture required for ovulation. Small studies in women treated with NSAIDs have also shown a reversible delay in ovulation. Consider withdrawal of NSAIDs, including VIOXX, in women who have difficulties conceiving or who are undergoing investigation of infertility.

Pediatric Use

The use of VIOXX in patients with pauciarticular or polyarticular course JRA ≥ 2 years to ≤ 17 years of age was studied in pharmacokinetic studies and a 12-week, double-blind active-controlled study with a 52-week open-label extension. (See CLINICAL PHARMACOLOGY, *Pediatric;* CLINICAL STUDIES, *Pediatric Patients, Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis (JRA);* ADVERSE REACTIONS*, Pauciarticular and Polyarticular Course JRA*.)

Rofecoxib has not been studied in patients under the age of 2 years, with body weight less than 10 kg (22 lbs.), or in children with systemic type JRA.

Geriatric Use

Elderly patients, compared to younger patients, are at greater risk for NSAID-associated serious cardiovascular, gastrointestinal, and/or renal adverse reactions. If the anticipated benefit for the elderly patient outweighs these potential risks, start dosing at the low end of the dosing range, and monitor patients for adverse effects (see the following subsections under WARNINGS: *Cardiovascular Thrombotic Events*; *Gastrointestinal Bleeding, Ulceration, and Perforation*; *Hepatotoxicity*; and *Renal Toxicity and Hyperkalemia*).

Of the patients who received VIOXX in osteoarthritis clinical trials, 1455 were 65 years of age or older. This included 460 patients who were 75 years or older, and in one of these studies, 174 patients who were 80 years or older. No substantial differences in safety and effectiveness were observed between these subjects and younger subjects. Greater sensitivity of some older individuals cannot be ruled out. As with other NSAIDs, including those that selectively inhibit COX-2, there have been more spontaneous post-marketing reports of fatal GI events and acute renal failure in the elderly than in younger patients. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.

ADVERSE REACTIONS

Osteoarthritis

Approximately 3600 patients with osteoarthritis were treated with VIOXX; 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 in OA Clinical Trials

	Placebo	VIOXX 12.5 or 25 mg daily	Ibuprofen 2400 mg daily	Diclofenac 150 mg daily
	(N = 783)	(N = 2829)	(N = 847)	(N = 498)
Body As A Whole/Site Unspecified				
Abdominal Pain	4.1	3.4	4.6	5.8
Asthenia/Fatigue	1.0	2.2	2.0	2.6
Dizziness	2.2	3.0	2.7	3.4
Influenza-Like Disease	3.1	2.9	1.5	3.2
Lower Extremity Edema	1.1	3.7	3.8	3.4
Upper Respiratory Infection	7.8	8.5	5.8	8.2
Cardiovascular System				
Hypertension	1.3	3.5	3.0	1.6
Digestive System				
Diarrhea	6.8	6.5	7.1	10.6
Dyspepsia	2.7	3.5	4.7	4.0
Epigastric Discomfort	2.8	3.8	9.2	5.4
Heartburn	3.6	4.2	5.2	4.6
Nausea	2.9	5.2	7.1	7.4
Eyes, Ears, Nose, And Throat				
Sinusitis	2.0	2.7	1.8	2.4
Musculoskeletal System				
Back Pain	1.9	2.5	1.4	2.8
Nervous System				
Headache	7.5	4.7	6.1	8.0

Respiratory System				
Bronchitis	0.8	2.0	1.4	3.2
Urogenital System				
Urinary Tract Infection	2.7	2.8	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, postoperative 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, hypersensitivity, 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: 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.

The following serious adverse events have been reported rarely (estimated <0.1%) in patients taking VIOXX, regardless of causality. Cases reported only in the post-marketing experience are indicated in italics.

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

Gastrointestinal: cholecystitis, colitis, colonic malignant neoplasm, *duodenal perforation*, duodenal ulcer, *esophageal ulcer*, *gastric perforation*, *gastric ulcer*, gastrointestinal bleeding, *hepatic failure*, *hepatitis*, intestinal obstruction, *jaundice*, pancreatitis.

Hemic and lymphatic: agranulocytosis, *aplastic anemia*, *leukopenia*, lymphoma, *pancytopenia*, *thrombocytopenia*.

Immune System: anaphylactic/anaphylactoid reaction, *angioedema*, *bronchospasm*, *hypersensitivity vasculitis*.

Metabolism and nutrition: hyponatremia.

Nervous System: aseptic meningitis, *epilepsy aggravated*.

Psychiatric: confusion, *hallucinations*.

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

Urogenital System: acute renal failure, breast malignant neoplasm, *hyperkalemia*, *interstitial nephritis*, prostatic malignant neoplasm, urolithiasis, *worsening chronic renal failure*.

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 1,100 patients were treated with VIOXX in the Phase III rheumatoid arthritis efficacy studies. These studies included extensions of up to 1 year. The adverse experience profile was generally similar to that reported in the osteoarthritis studies. In studies of at least three months, the incidence of hypertension in RA patients receiving the 25 mg once daily dose of VIOXX was 10.0% and the incidence of hypertension in patients receiving naproxen 500 mg twice daily was 4.7%.

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).

Migraine with or without aura

Approximately 750 patients were treated with a single dose of VIOXX 25 mg or 50 mg in two single-attack migraine studies. Approximately 460 patients in the 3-month extension phase of one study treated up to 8 (average 3) migraine attacks per month. In single attack studies, the following adverse events were more frequent in the VIOXX treatment groups (25 mg and 50 mg) compared to the placebo group, and occurred at an incidence of at least 2% of patients treated: dizziness, nausea, somnolence and dyspepsia. In the 3-month extension phase of one study, the following adverse events occurred at an incidence of at least 2% of patients treated in the VIOXX treatment groups (25 mg and 50 mg): dizziness, dry mouth, nausea, and vomiting.

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

In OA and RA clinical trials which contained VIOXX 12.5 or 25 mg as well as VIOXX 50 mg, VIOXX 50 mg QD 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 discontinuation due to clinical adverse experiences compared to the recommended chronic doses of 12.5 and 25 mg (see DOSAGE AND ADMINISTRATION).

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis

In a 12-week study, 209 JRA patients, $\geq$ 2 years to $\leq$ 17 years of age, were treated with rofecoxib; 109 and 100 patients were treated with lower-dose rofecoxib and higher-dose rofecoxib, respectively. In a 52-week open-label extension, 160 JRA patients, $\geq$ 2 years to $\leq$ 17 years of age, were treated with higher-dose rofecoxib for up to 15 months. No new adverse experiences were identified other than a single case of pseudoporphyria (a photo-induced blistering reaction), an adverse event that has been seen in patients with JRA treated with non-selective NSAIDs. In this 12-week study, the most common adverse experiences (at 0.6 mg/kg dose) were upper abdominal pain, nasopharyngitis, diarrhea, upper respiratory tract infection, abdominal pain, headache and rhinitis. Rash was also reported.

OVERDOSAGE

Symptoms following acute NSAID overdosages have been typically limited to lethargy, drowsiness, nausea, vomiting, and epigastric pain, which have been generally reversible with supportive care. Gastrointestinal bleeding has occurred. Hypertension, acute renal failure, respiratory depression, and

*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

coma have occurred, but were rare. (See WARNINGS, *Cardiovascular Thrombotic Events* and WARNINGS, *Gastrointestinal Bleeding, Ulceration, and Perforation*).

No overdoses of VIOXX were reported during clinical trials. Administration of single doses of VIOXX 1000 mg to 6 healthy volunteers and multiple doses of 250 mg/day for 14 days to 75 healthy volunteers did not result in serious toxicity.

Manage patients with symptomatic and supportive care following an NSAID overdosage. There are no specific antidotes. Consider emesis and/or activated charcoal (60 to 100 grams in adults, 1 to 2 grams per kg of body weight in pediatric patients) and/or osmotic cathartic in symptomatic patients seen within four hours of ingestion or in patients with a large overdosage (5 to 10 times the recommended dosage). Forced diuresis, alkalinization of urine, hemodialysis, or hemoperfusion may not be useful due to high protein binding.

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

For additional information about overdosage treatment contact a poison control center (1-800-222-1222).

DOSAGE AND ADMINISTRATION

VIOXX is administered orally. Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals (see WARNINGS).

Osteoarthritis

The recommended starting dose of VIOXX 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.

Rheumatoid Arthritis

The recommended dose is 25 mg once daily. The maximum recommended daily dose is 25 mg.

Pauciarticular and Polyarticular Course Juvenile Rheumatoid Arthritis

Pediatric Patients	**Daily Dose**
≥ 2 years to ≤ 11 years of age and ≥ 10 to < 42 kg	0.6 mg/kg to a maximum of 25 mg*
≥ 2 years to ≤ 11 years of age and ≥ 42 kg	25 mg
≥ 12 years to ≤ 17 years of age	25 mg

*Oral suspension dosage form is recommended. To improve dosing accuracy in smaller weight children, the use of 12.5 mg/5 mL oral suspension (2.5 mg/mL) is recommended.

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended dose of VIOXX is 50 mg once daily. The maximum recommended daily dose is 50 mg. Use of VIOXX for more than 5 days in management of pain has not been studied. Chronic use of VIOXX 50 mg daily is not recommended. (See ADVERSE REACTIONS, *Clinical Studies in OA and RA with VIOXX 50 mg*).

Acute Treatment of Migraine Attacks with or without aura

The recommended starting dose of VIOXX is 25 mg once daily. Some patients may receive additional benefit with 50 mg as compared to 25 mg. The maximum recommended daily dose is 50 mg. The safety of treating more than 5 migraine attacks in any given month has not been established. Chronic daily use of VIOXX for the acute treatment of migraine is not recommended.

Hepatic Impairment

Because of significant increases in both AUC and C_{max} in patients with moderate hepatic impairment (Child-Pugh score: 7-9), the maximum recommended chronic daily dose is 12.5 mg. (See CLINICAL PHARMACOLOGY, *Special Populations*). The efficacy of 12.5 mg in rheumatoid arthritis patients with

moderate hepatic insufficiency has not been studied. Use of VIOXX is not recommended in patients with severe hepatic insufficiency.

VIOXX Tablets 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. Shake before using.

HOW SUPPLIED

No. 3810 — Tablets VIOXX, 12.5 mg, are cream/off-white, round, shallow cup tablets engraved MRK 74 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0074-31 unit of use bottles of 30
NDC 0006-0074-28 unit dose packages of 100
NDC 0006-0074-68 bottles of 100
NDC 0006-0074-82 bottles of 1000
NDC 0006-0074-80 bottles of 8000.

No. 3834 — Tablets VIOXX, 25 mg, are yellow, round tablets engraved MRK 110 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0110-31 unit of use bottles of 30
NDC 0006-0110-28 unit dose packages of 100
NDC 0006-0110-68 bottles of 100
NDC 0006-0110-82 bottles of 1000
NDC 0006-0110-80 bottles of 8000.

No. 3835 — Tablets VIOXX, 50 mg, are orange, round tablets engraved MRK 114 on one side and VIOXX on the other. They are supplied as follows:

NDC 0006-0114-31 unit of use bottles of 30
NDC 0006-0114-28 unit dose packages of 100
NDC 0006-0114-68 bottles of 100
NDC 0006-0114-74 bottles of 500
NDC 0006-0114-81 bottles of 4000.

No. 3784 — Oral Suspension VIOXX, 12.5 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking.

NDC 0006-3784-64 unit of use bottles containing 150 mL (12.5 mg/5 mL).

No. 3785 — Oral Suspension VIOXX, 25 mg/5 mL, is an opaque, white to faint yellow suspension with a strawberry flavor that is easily resuspended upon shaking.

NDC 0006-3785-64 unit of use bottles containing 150 mL (25 mg/5 mL).

Storage

VIOXX Tablets:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

VIOXX Oral Suspension:

Store at 25°C (77°F), excursions permitted to 15-30°C (59-86°F). [See USP Controlled Room Temperature.]

Rx only

Merck Sharp & Dohme Corp., a subsidiary of
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Medication Guide for Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?

NSAIDs can cause serious side effects, including:

- **Increased risk of a heart attack or stroke that can lead to death**. This risk may happen early in treatment and may increase:
  - with increasing doses of NSAIDs
  - with longer use of NSAIDs

  Do not take NSAIDs right before or after a heart surgery called a "coronary artery bypass graft (CABG)."

  Avoid taking NSAIDs after a recent heart attack, unless your healthcare provider tells you to. You may have an increased risk of another heart attack if you take NSAIDs after a recent heart attack.
- **Increased risk of bleeding, ulcers, and tears (perforation) of the esophagus (tube leading from the mouth to the stomach), stomach and intestines:**
  - anytime during use
  - without warning symptoms
  - that may cause death

  The risk of getting an ulcer or bleeding increases with:
  - past history of stomach ulcers, or stomach or intestinal bleeding with use of NSAIDs
  - taking medicines called "corticosteroids", "anticoagulants", "SSRIs", or "SNRIs"
  - increasing doses of NSAIDs
  - longer use of NSAIDs
  - smoking
  - drinking alcohol
  - older age
  - poor health
  - advanced liver disease
  - bleeding problems

NSAIDs should only be used:
- exactly as prescribed
- at the lowest dose possible for your treatment
- for the shortest time needed

What are NSAIDs?

NSAIDs are used to treat pain and redness, swelling, and heat (inflammation) from medical conditions such as different types of arthritis, menstrual cramps, and other types of short-term pain.

Who should not take NSAIDs?

Do not take NSAIDs:
- if you have had an asthma attack, hives, or other allergic reaction with aspirin or any other NSAIDs.
- right before or after heart bypass surgery.

Before taking NSAIDs, tell your healthcare provider about all of your medical conditions, including if you:
- have liver or kidney problems
- have high blood pressure
- have asthma
- are pregnant or plan to become pregnant. Talk to your healthcare provider if you are considering taking NSAIDs during pregnancy. **You should not take NSAIDs after 29 weeks of pregnancy.**
- are breastfeeding or plan to breast feed.

Tell your healthcare provider about all of the medicines you take, including prescription or over-the-counter medicines, vitamins or herbal supplements. NSAIDs and some other medicines can interact with each other and cause serious side effects. **Do not start taking any new medicine without talking to your healthcare provider first.**

What are the possible side effects of NSAIDs?

NSAIDs can cause serious side effects, including:

See "What is the most important information I should know about medicines called Nonsteroidal Anti-inflammatory Drugs (NSAIDs)?
- new or worse high blood pressure
- heart failure
- liver problems including liver failure

- kidney problems including kidney failure
- low red blood cells (anemia)
- life-threatening skin reactions
- life-threatening allergic reactions
- **Other side effects of NSAIDs include:** stomach pain, constipation, diarrhea, gas, heartburn, nausea, vomiting, and dizziness.

Get emergency help right away if you get any of the following symptoms:

- shortness of breath or trouble breathing
- chest pain
- weakness in one part or side of your body
- slurred speech
- swelling of the face or throat

Stop taking your NSAID and call your healthcare provider right away if you get any of the following symptoms:

- nausea
- more tired or weaker than usual
- diarrhea
- itching
- your skin or eyes look yellow
- indigestion or stomach pain
- flu-like symptoms
- vomit blood
- there is blood in your bowel movement or it is black and sticky like tar
- unusual weight gain
- skin rash or blisters with fever
- swelling of the arms, legs, hands and feet

If you take too much of your NSAID, call your healthcare provider or get medical help right away.

These are not all the possible side effects of NSAIDs. For more information, ask your healthcare provider or pharmacist about NSAIDs.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Other information about NSAIDs

- Aspirin is an NSAID but it does not increase the chance of a heart attack. Aspirin can cause bleeding in the brain, stomach, and intestines. Aspirin can also cause ulcers in the stomach and intestines.
- Some NSAIDs are sold in lower doses without a prescription (over-the-counter). Talk to your healthcare provider before using over-the-counter NSAIDs for more than 10 days.

General information about the safe and effective use of NSAIDs

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use NSAIDs for a condition for which it was not prescribed. Do not give NSAIDs to other people, even if they have the same symptoms that you have. It may harm them.

If you would like more information about NSAIDs, talk with your healthcare provider. You can ask your pharmacist or healthcare provider for information about NSAIDs that is written for health professionals.

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