

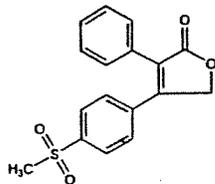
 **MERCK & CO., INC.**
Whitehouse Station, NJ 08889, USA

9183806

VIOXX®
(rofecoxib tablets and oral suspension)

DESCRIPTION

VIOXX® (rofecoxib) is described chemically as 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone. 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. The empirical formula for rofecoxib is C₁₇H₁₄O₃S, and the molecular weight is 314.36.

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.

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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

VIOXX is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. The mechanism of action of VIOXX is believed to be due to inhibition of prostaglandin synthesis, via inhibition of cyclooxygenase-2 (COX-2). At therapeutic concentrations in humans, VIOXX does not inhibit the cyclooxygenase-1 (COX-1) isoenzyme.

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_{0-24hr} 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. 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

Merck accepts proposal to re-instate currently approved text.

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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 mcg/mL. The apparent volume of distribution at steady state (V_{ss}) 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.

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. (Also see *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.,

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non-linear elimination). The effective half-life (based on steady-state levels) was approximately 17 hours.

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.

Pediatric

VIOXX has not been investigated in patients below 18 years of age.

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 pharmacokinetic study in mild (Child-Pugh score ≤ 6) hepatic insufficiency patients indicated that rofecoxib AUC was similar between these patients and healthy subjects. Limited data in patients with moderate (Child-Pugh score 7-9) hepatic insufficiency suggest a trend towards higher AUC (about 69%) of rofecoxib in these patients, but more data are needed to evaluate pharmacokinetics in these patients. Patients with severe hepatic insufficiency have not been studied.

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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. ~~— Severe renal failure including fatalities and need for dialysis has been reported in post-marketing in association with VIOXX. (See PRECAUTIONS). (See WARNINGS, Advanced Renal Disease.)~~

Drug Interactions (Also 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 rofecoxib have identified potentially significant interactions with rifampin, methotrexate 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.

Merck accepts deletion of text stating that no information is available in patients with advanced renal disease and has revised text under WARNINGS, *Advanced Renal Disease* for consistency.

Merck proposes to delete. Consistent with NSAID class labeling, this information is provided in other parts of the circular. Merck proposes to add appropriate cross-reference.

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CLINICAL STUDIES

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.

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 ~~one hour~~. 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

Merck proposes to retain currently approved text. The time to onset is based on the Agency standard (2-stopwatch method) and is accurately described in the approved label as negotiated with the Agency. No new analgesia data have been provided in the VIGOR submission to suggest any alteration of the description for time to onset.

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placebo (1.5 versus 2.5 doses per day of additional analgesic medication for VIOXX and placebo, respectively). ~~In acute pain studies, median time to re-medication was between 5.3 and 9.5 hours. VIOXX 50 mg should not be given more than once daily. If additional analgesia is needed within 24 hour of dose, alternative therapy should be used. Chronic use of VIOXX 50 mg daily is not recommended.~~

The Agency's proposed additions of data on re-medication and the recommendation for dosing within the approved dosing interval are inconsistent with the labeling of other NSAID analgesics and are not based on any new analgesia data since the time the approved labeling was negotiated.

Special Studies

Safety Studies

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

Merck proposes to delete new heading "Safety Studies". Merck proposes to delete sentence since VIGOR was not a general safety study.

VIOXX GI Clinical Outcomes Research (VIGOR Study)

Study Design

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 received VIOXX 50 mg once daily (the approved dose for the treatment of acute pain and twice the highest dose recommended for chronic use in OA) or naproxen 500 mg twice daily a-day (common therapeutic dose). The VIGOR study was designed primarily to evaluate the comparative GI safety of VIOXX 50 mg once daily versus naproxen 500 mg twice daily. The GI safety endpoints included: the comparative rate of all clinical upper GI events,* complicated upper GI events** and GI bleeding***. 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. Of the patients who received VIOXX, 997 were 65 years of age and older (this included 197 who were 75 years or older). Fifty-six percent of patients used concomitant oral corticosteroids. ~~The study included GI safety endpoints: the rate of complicated** ulcers and the combined rate of complicated and uncomplicated** ulcers; and general safety endpoints.~~

Merck accepts with revisions as shown.

* ~~Complicated ulcers: upper GI perforation, obstruction or bleed (PUB's)~~

** ~~Uncomplicated ulcer: symptomatic ulcer~~

* All clinical upper GI events: complicated upper GI events, symptomatic ulcers and minor bleeding (PUB's).

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- ** ~~Complicated upper GI events: upper GI perforation, obstruction or major bleeding (complicated PUBs).~~
- *** ~~GI bleeding: upper and/or lower GI bleeding.~~

Results

Overall safety in VIGOR

~~No statistically significant differences were seen between VIOXX and naproxen in the overall incidences of deaths, withdrawals due to adverse events and serious adverse events (i.e. those causing hospitalization or felt to be life threatening or otherwise medically significant).~~

Merck proposes to delete the "Overall safety in VIGOR" sub-section. This study was primarily designed to evaluate the GI safety of VIOXX at 2 times the maximum chronic dose. General safety information is provided in the ADVERSE REACTIONS section.

~~Table 3. VIGOR SUMMARY OF General SAFETY EVENTS by body system~~

~~(Events with incidence of at least 2% in any treatment group)~~

	VIOXX 50 mg N= 4047	Naproxen 500mg bid N= 4029
% of patients who died	0.5	0.4
% of patients with one or more Serious AEs	9.3	7.8
Cardiovascular System	2.5	1.1
Digestive system	1.2	2.4
Musculoskeletal system	2.1	1.7
% of patients with one or more Discontinuations due to AEs	15.0	15.8
Body as a Whole	2.5	2.7
Cardiovascular System	2.7	0.8
Digestive system	7.2	9.7

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Gastrointestinal Safety in VIGOR

The study demonstrated a significant reduction in the risk of development of ~~complicated~~
PUBs, including complicated PUBs, as well as GI bleeding, ~~combined complicated and~~
~~uncomplicated~~ PUBs, in patients taking VIOXX compared to naproxen (see Table 1).

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**Table 4. VIGOR—COMPARISON TO NAPROXEN
SUMMARY OF GI SAFETY EVENTS**

GI
SPONSOR TO PROVIDE TABLE WITH CUMULATIVE RATES, RELATIVE RISKS AND BOTH P AND CI FOR PUBS AND COMPLICATED PUBS (NOT "ANY GI BLEED").

**Table 1
VIGOR—Summary of Gastrointestinal Safety Events¹
COMPARISON TO NAPROXEN**

Event	Treatment	Rates ²	Relative Risk	95% CI	p-value
PUBs	Rofecoxib	2.08	0.46	(0.33, 0.64)	<u><0.001</u>
	Naproxen	4.49			
Clinically-Complicated PUBs	Rofecoxib	0.59	0.43	(0.24, 0.78)	<u>0.005</u>
	Naproxen	1.37			
GI Bleeding	Rofecoxib	<u>1.15</u>	<u>0.38</u>	<u>(0.25, 0.57)</u>	<u><0.001</u>
	Naproxen	<u>3.04</u>			

¹As confirmed by an independent committee blinded to treatment

²Per 100 patient years

The GI safety advantage of VIOXX compared to naproxen was maintained in the following subgroups of patients at higher risk—subgroup for developing a PUB: patients with a prior history of a PUB, patients with *Helicobacter pylori* infection, elderly patients and patients taking corticosteroids. A similar safety advantage was seen in patients without any of these risk factors. (See Table 2.)

Merck accepts proposal to delete "Risk Reduction" from the GI safety table. However, Merck proposes to retain "GI Bleeding" data in the GI safety table as it was a pre-specified endpoint and provides important information relative to other warnings in the circular.

Merck accepts with revisions and proposes addition of second sentence.

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SPONSOR TO PROVIDE NUMBERS FOR ALL OF THESE.

Merck accepts and provides Table 2. Note that the low-risk subgroups have been combined for brevity.

Table 2
VIGOR-Summary of Gastrointestinal Safety Events¹
By Risk Subgroups²
COMPARISON TO NAPROXEN

<u>Subgroup²</u>	<u>Treatment</u>	<u>Rates³</u>	<u>Relative Risk</u>	<u>95% CI</u>	<u>p-value</u>
<u>Patients with a prior history of a PUD</u>	<u>Rofecoxib</u>	<u>6.72</u>	<u>0.44</u>	<u>(0.23, 0.85)</u>	<u>0.015</u>
	<u>Naproxen</u>	<u>15.33</u>			
<u>Patients with H. pylori infection</u>	<u>Rofecoxib</u>	<u>2.87</u>	<u>0.62</u>	<u>(0.40, 0.95)</u>	<u>0.029</u>
	<u>Naproxen</u>	<u>4.62</u>			
<u>Patients 65 years of age or older</u>	<u>Rofecoxib</u>	<u>3.54</u>	<u>0.41</u>	<u>(0.25, 0.67)</u>	<u><0.001</u>
	<u>Naproxen</u>	<u>8.63</u>			
<u>Patients with baseline corticosteroid use</u>	<u>Rofecoxib</u>	<u>2.11</u>	<u>0.37</u>	<u>(0.25, 0.56)</u>	<u><0.001</u>
	<u>Naproxen</u>	<u>5.67</u>			
<u>Patients without any of these risk factors</u>	<u>Rofecoxib</u>	<u>0.22</u>	<u>0.12</u>	<u>(0.02, 0.96)</u>	<u>0.046</u>
	<u>Naproxen</u>	<u>1.85</u>			

¹As confirmed by an independent committee blinded to treatment

²Based on risk for developing a PUD

³Per 100 patient years at risk

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Cardiovascular Safety in VIGOR

~~The VIGOR study demonstrated a significant increase in the risk of development of serious cardiovascular thrombotic events in patients taking VIOXX (n=64) compared to naproxen (n=32) (see Table 5). In the VIGOR study, there was a significant difference in the incidence of serious cardiovascular thrombotic events between patients treated with VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA) and patients treated with naproxen 500 mg twice daily (common therapeutic dose). Serious cardiovascular thrombotic events included cardiac events*, cerebrovascular events** and peripheral vascular events*** (See Table 3.)~~

- * ~~Cardiac events included acute myocardial infarction, unstable angina and sudden cardiac death.~~
- ** ~~Cerebrovascular events included stroke and transient ischemic attacks (TIA).~~
- *** ~~Peripheral vascular events included peripheral arterial and peripheral venous thromboses.~~

~~Table 5. VIGOR—COMPARISON TO NAPROXEN
SUMMARY OF Cardiovascular SAFETY EVENTS~~

~~Table: VIGOR—Investigator's reported serious cardiovascular thrombotic adverse events by category~~

Merck proposes new text regarding the cardiovascular safety in VIGOR.

Merck proposes to replace investigator-reported events with the pre-specified endpoint of adjudicated events.

See table below.

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N	Cumulative Rate	Relative risk*	CI	p-value
All patients	VIOXX 50 mg	64		
	Naproxen	32		
<u>Cardiac</u>				
	VIOXX 50 mg	36		
	Naproxen	24		
<u>Cerebrovascular</u>				
	VIOXX 50 mg	29		
	Naproxen	9		
<u>Peripheral</u>				
	VIOXX 50 mg	8		
	Naproxen	2		

RR of VIOXX relative to naproxen:

SPONSOR TO PROVIDE CUMULATIVE RATE OF INVESTIGATOR REPORTED SERIOUS CV THROMBOTIC EVENTS AND ANALYSES BY CATEGORY

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Table 3
VIGOR-Summary of Serious Cardiovascular Thrombotic Adverse Events¹
COMPARISON TO NAPROXEN

<u>Event Category</u>	<u>Treatment</u>	<u>Rates²</u>	<u>Relative Risk</u>	<u>95% CI</u>	<u>p-value</u>
<u>All thrombotic events</u>	<u>Rofecoxib</u>	<u>1.67</u>	<u>2.37</u>	<u>(1.39, 4.06)</u>	<u>0.002</u>
	<u>Naproxen</u>	<u>0.70</u>			
<u>Cardiac events</u>	<u>Rofecoxib</u>	<u>1.04</u>	<u>2.80</u>	<u>(1.36, 5.77)</u>	<u>0.005</u>
	<u>Naproxen</u>	<u>0.37</u>			
<u>Cerebrovascular events</u>	<u>Rofecoxib</u>	<u>0.41</u>	<u>1.38</u>	<u>(0.55, 3.43)</u>	<u>0.489</u>
	<u>Naproxen</u>	<u>0.30</u>			
<u>Peripheral vascular events</u>	<u>Rofecoxib</u>	<u>0.22</u>	<u>6.00</u>	<u>(0.73, 276.0)</u>	<u>0.058</u>
	<u>Naproxen</u>	<u>0.04</u>			

¹As confirmed by an independent committee blinded to treatment
²Per 100 patient years at risk

The excess of cardiovascular thrombotic events on VIOXX compared to naproxen was more marked in the subgroup of patients retrospectively identified as being at high risk for cardiovascular disease (see Table 6).

Merck proposes to delete. Updated data submitted to the Agency on 13 Oct 2000 demonstrate that the relative risk of an event for rofecoxib relative to naproxen is not statistically different between the aspirin-indicated and aspirin-not-indicated sub-populations.

Table 6. VIGOR - COMPARISON TO NAPROXEN
SUMMARY OF Cardiovascular SAFETY EVENTS by ASA use

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	N	Cumulative Rate	Relative risk*	CI	p-value
All patients	VIOXX 50 mg 64				
	Naproxen 32				
Patients at high risk for CV disease					
	VIOXX 50 mg				
	Naproxen				
Patients with no risk for CV disease					
	VIOXX 50 mg				
	Naproxen				

** Definition

SPONSOR TO PROVIDE CUMULATIVE RATES OF INVESTIGATOR REPORTED SERIOUS THROMBOTIC EVENTS AND ANALYSES BY ASA USE

~~In addition to the CV thrombotic events, VIOXX 50 mg had a higher incidence of discontinuations due to HTN and edema related events as well as congestive heart failure events as compared to naproxen.~~

Updated data demonstrate that the relative risk of an event for rofecoxib relative to naproxen is not statistically different between the aspirin-indicated and aspirin-not-indicated sub-populations.

Merck proposes to delete. Hypertension and edema-related events are adequately covered by NSAID class labeling in this circular. This section is not the appropriate place to discuss CHF; it is addressed in the ADVERSE REACTIONS section. In addition, these adverse experiences were not associated with cardiovascular thrombotic events in the VIGOR study.

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Combined Analysis in OA Patients

In a combined analysis of PUBs from all Phase IIb/III clinical trials in OA patients, the reduction in risk for a PUB in the combined group of patients treated with VIOXX 12.5, 25 and 50 mg daily was similar to that described in RA patients in the VIGOR study. In these OA studies, most of the risk reduction in the patients treated with VIOXX occurred in the studies in which ibuprofen was the comparator. In these OA studies, the rates of patients having serious cardiovascular thrombotic events was determined in the VIOXX (N=1701, 363 patient-years) and placebo (N=514, 127 patient-years) studies and in the VIOXX (N=3358, 2372 patient-years) and nonselective NSAID (N=1565, 1026 patient-years) studies. The nonselective NSAID studies included ibuprofen, diclofenac, and nabumetone. In the placebo-controlled studies, serious cardiovascular thrombotic events in patients treated with VIOXX occurred in 2.5 patients per 100 patient-years (9 patients had events: 4 cardiac, 4 cerebrovascular and 1 peripheral vascular) versus 2.4 per 100 patient-years for the placebo group (3 patients had events: 2 cardiac and 1 cerebrovascular). In the nonselective NSAID-controlled studies, serious cardiovascular thrombotic events in patients treated with VIOXX occurred in 2.1 patients per 100 patient-years (49 patients had events: 28 cardiac, 14 cerebrovascular and 7 peripheral vascular) versus 2.1 per 100 patient-years for the nonselective NSAID group (21 patients had events: 14 cardiac, 5 cerebrovascular and 2 peripheral vascular).

Study 402003 (ADVANTAGE study) The ADVANTAGE Study

ADVANTAGE was a 3-month trial that compared the use of VIOXX 25 mg once daily to naproxen 500 mg twice daily a day in patients with osteoarthritis (N=5,500-5,559). It showed a similar pattern of overall, GI and CV safety observed in VIGOR. This study allowed the use of low-dose ASA. Approximately 13% of patients used low-dose aspirin in this study. There was one complicated PUB in the VIOXX 25 mg group compared to four complicated PUBs in the naproxen group. There were nine patients with serious cardiovascular thrombotic events (8 cardiac and 1 cerebrovascular) 6-MI, one unstable angina and 3 sudden deaths) in the VIOXX 25 mg group, compared to 3, 12 patients with cardiac serious cardiovascular thrombotic events (3 cardiac, 7 cerebrovascular and 2 peripheral vascular) 2-unstable-angina, one-MI) in the naproxen group.

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Merck proposes to retain 069 GI data as per prior agreement during the label negotiations for the initial VIOXX NDA. These results provide useful information that are consistent with the VIGOR data in a different patient population (OA) and with different comparators.

Merck proposes revisions as shown. It is more appropriate to include comparison of all cardiovascular thrombotic events as the Agency requested for the VIGOR study.

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Ongoing Placebo-Controlled Studies

Three placebo-controlled studies (mean and median duration of approximately 1 year) in a total of 2899 patients (mean age 75 years) are being conducted with VIOXX 25 mg once daily. In an interim analysis of cardiovascular safety data from these studies, there were 25 patients with serious cardiovascular thrombotic events (14 cardiac and 11 cerebrovascular) in the VIOXX 25 mg group compared to 39 patients with serious cardiovascular thrombotic events (20 cardiac, 16 cerebrovascular and 3 peripheral vascular) in the placebo group.

Upper Endoscopy in Patients with Osteoarthritis

~~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 these studies are of less clinical relevance than the outcomes identified in the VIGOR study (See 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.

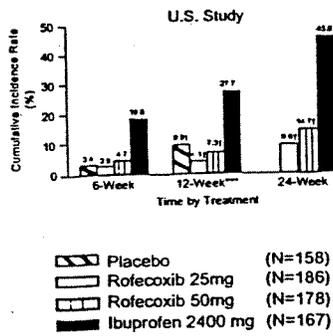
Treatment with VIOXX 25 mg daily or 50 mg daily was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. However, the studies cannot rule out at least some increase in the rate of endoscopic gastroduodenal ulcers when comparing VIOXX to placebo. See Figures 1 and 2 and the accompanying tables for the results of these studies.

Merck proposes addition of Alzheimer's Disease study data to include information on cardiovascular thrombotic events compared to placebo.

Merck proposes to delete. Consistent with the Agency's well-established precedents, the successful completion of an outcomes study serves to validate surrogates, not diminish them.

Figure 1

COMPARISON TO IBUPROFEN
 Life-Table Cumulative Incidence Rate of Gastroduodenal
 Ulcers $\geq 3\text{mm}^*$ (Intention-to-Treat)



* $p < 0.001$ versus ibuprofen 2400 mg
 — Results of analyses using a $\geq 2.5\text{mm}$ gastroduodenal ulcer endpoint were consistent.
 — The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

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TABLE 4j
Endoscopic Gastrointestinal Ulcers at 12 weeks
U.S. Study

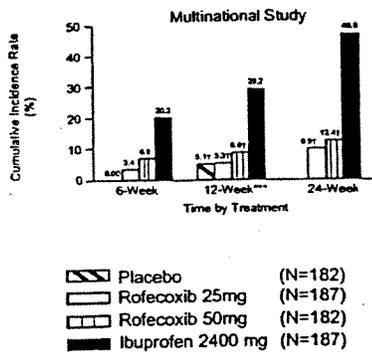
Treatment Group	Number of Patients with Ulcer/Total Number of Patients	Cumulative Incidence Rate*	Ratio of Rates vs. Placebo	95% CI on Ratio of Rates
Placebo	11/158	9.9%	—	—
VIOXX 25 mg	7/186	4.1%	0.41	(0.16, 1.05)
VIOXX 50 mg	12/178	7.3%	0.74	(0.33, 1.64)
Ibuprofen	42/167	27.7%	2.79	(1.47, 5.30)

*by life table analysis

Figure 2

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers $\geq 3\text{mm}^*$ (Intention-to-Treat)



* p < 0.001 versus ibuprofen 2400 mg
 — Results of analyses using a $\geq 5\text{mm}$ gastroduodenal ulcer endpoint were consistent.
 — The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

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TABLE 25
 Endoscopic Gastrointestinal 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	5/182	5.1%	-	-
VIOXX 25 mg	9/187	5.3%	1.04	(0.36, 3.01)
VIOXX 50 mg	15/182	8.8%	1.73	(0.65, 4.61)
Ibuprofen	49/187	29.2%	5.72	(2.36, 13.89)

*by life table analysis

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

Merck accepts proposal to re-instate this portion of the currently approved text.

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 ⁵¹Cr-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.

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Use with Aspirin

In 4 six- to twelve-week double-blind randomized clinical trials, VIOXX 12.5 mg or 25 mg was administered to osteoarthritis patients concomitantly with aspirin (less than or equal to 325 mg daily) (N=516). Among these 516 patients, there was 1 PUB. While low-dose aspirin may be used concomitantly with VIOXX, such concomitant use may result in an increased rate of GI ulceration or other complications, compared to use of VIOXX alone. (See PRECAUTIONS, Cardiovascular Effects and PRECAUTIONS, Drug Interactions, Aspirin.)

Merck proposes to retain subsection that was submitted and update with current available information. Previous agreement with the Division was that concomitant use of VIOXX with aspirin in 100 patients or more would be sufficient to allow a recommendation for concomitant use. With the Agency's request to include ADVANTAGE data in the CLINICAL STUDIES section, data on concomitant use of VIOXX with aspirin now includes over 500 patients. This markedly enhances the experience of patients taking VIOXX concomitantly with aspirin to a level beyond that noted in labeling for other members of the class.

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. (See PRECAUTIONS, Cardiovascular Effects.)

Merck is uncertain as to why the Agency has deleted this previously approved text regarding the single-dose study. Nonetheless, Merck accepts this deletion. Merck proposes to add appropriate cross-reference.

~~Because of its lack of platelet effects, VIOXX is not a substitute for aspirin in patients requiring cardiovascular prophylaxis. (bold)~~

Merck proposes to relocate to PRECAUTIONS, Cardiovascular Effects.

INDICATIONS AND USAGE

VIOXX is indicated:

- For relief of the signs and symptoms of osteoarthritis.
- For the management of acute pain in adults (see CLINICAL STUDIES).
- For the treatment of primary dysmenorrhea.

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CONTRAINDICATIONS

VIOXX 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 aspirin or other NSAIDs. Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, *Anaphylactoid Reactions* and PRECAUTIONS, *Preexisting Asthma*).

WARNINGS

Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding, and Perforation

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.

~~In the VIOXX GI outcomes research (VIGOR) study, the cumulative incidence of PUGs with VIOXX 50 mg the approved dose for the treatment of acute pain and twice the maximum dose recommended for chronic use in osteoarthritis was 1.8% over a median exposure of 9 months. (See CLINICAL STUDIES, Special Studies, Safety Studies, VIGOR.)~~

In the VIOXX GI outcomes research (VIGOR) study, the risk of development of a PUG was 54% lower in rheumatoid arthritis patients treated with VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA) than in patients treated with naproxen

Merck accepts proposal to re-instate currently approved text.

Merck proposes revisions as shown.

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500 mg twice daily (common therapeutic dose) (see CLINICAL STUDIES, Special Studies, VIGOR).

In a combined analysis of PUBs from all Phase IIb/III clinical trials in OA patients, the reduction in risk for a PUB in patients treated with VIOXX was similar to that described in RA patients in the VIGOR study. In these OA studies, most of the risk reduction in the patients treated with VIOXX occurred in the studies in which ibuprofen was the comparator.

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. 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.

Previous 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.

SPONSOR TO PROVIDE TABLES OF CUMULATIVE INCIDENCES OF COMPLICATED AND UNCOMPLICATED ULCERS IN VIGOR IN

1. SUBJECTS UNDER AND OVER THE AGE OF 65
2. SUBJECTS WITH AND WITHOUT A HISTORY OF SYMPTOMATIC UPPER GI ULCERS

Merck proposes to retain 069 GI data as per prior agreement during the label negotiations for the initial VIOXX NDA. These results provide useful information that are consistent with the VIGOR data in a different patient population (OA) and with different comparators.

Merck accepts addition of the word "previous."

Merck has added the information on patients greater than 65 years of age and patients with a prior history of a PUB to Table 2 of the CLINICAL STUDIES section. Note that the low-risk subgroups have been combined for brevity.

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Cardiovascular Disease

~~VIOXX should be used with caution in patients at risk of developing cardiovascular thrombotic events such as those with a history of myocardial infarction and angina and in patients with pre-existent hypertension and congestive heart failure.~~

~~The risk of developing myocardial infarction in the VIGOR study was five-fold higher in patients treated with VIOXX 50 mg (0.5%) as compared to patients treated with naproxen (0.1%) (See Special studies, VIGOR). The finding was consistent in a smaller and shorter study using VIOXX 25 mg that allowed the use of low-dose ASA (See Special Studies, ADVANTAGE). Prospective, well-powered, long-term studies required to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators other than naproxen have not been performed.~~

~~Because of its lack of platelet effect, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. The impact of VIOXX on the cardiovascular prophylactic benefit of ASA is unknown. (See special studies, Platelets; PRECAUTIONS, Drug Interactions, Aspirin).~~

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 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 aspirin or other NSAIDs (see CONTRAINDICATIONS and PRECAUTIONS, *Preexisting Asthma*). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

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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 with advanced renal disease. In post-marketing experience, serious renal failure, including the need for dialysis and fatalities have been reported in patients with normal, as well as impaired renal function. These events may occur after short term therapy. If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, Renal Effects).~~

Pregnancy

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

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.

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.

Hepatic Effects

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

Merck proposes to update based upon post-marketing data and for consistency with CLINICAL PHARMACOLOGY, *Special Populations, Renal Insufficiency.*

Merck proposes to delete. As for all NSAIDs, this information is provided in other parts of the circular.

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trials, approximately 0.5% of patients taking rofecoxib (12.5 or 25 mg QD) 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 test has occurred, should be monitored carefully for evidence of the development of a more severe hepatic reaction while on therapy with VIOXX. Use of VIOXX is not recommended in patients with moderate or severe hepatic insufficiency (see *Pharmacokinetics, Special Populations*). If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), VIOXX should be discontinued.

Renal Effects

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 ACE inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. ~~However, severe renal failure including fatalities and need for dialysis have been reported in post-marketing in association with VIOXX. (See WARNINGS, Advanced renal disease).~~

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*).

Merck proposes to delete. Consistent with NSAID class labeling, this information is provided in other parts of the circular.

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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; these occur with an increased frequency with chronic use of VIOXX at doses above the 12.5 to 25 mg range. (See ADVERSE REACTIONS.) ~~New-onset of congestive heart failure, worsening of pre-existing congestive heart failure and severe pulmonary edema have been reported in post-marketing in association with the use of VIOXX at recommended doses. VIOXX should be used with caution, and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.~~

Cardiovascular Effects

The risk of developing a serious cardiovascular thrombotic event in the VIGOR study was significantly different in patients treated with VIOXX 50 mg once daily (twice the highest dose recommended for chronic use in OA) as compared to patients treated with naproxen 500 mg twice daily (common therapeutic dose). This was largely due to the significant difference in the incidence of myocardial infarction between patients taking VIOXX 50 mg once daily (0.5%) and naproxen 500 mg twice daily (0.1%). (See CLINICAL STUDIES, Special Studies, VIGOR.) In all other controlled clinical trials, the incidence of all serious cardiovascular thrombotic events, including myocardial infarction, was similar between VIOXX and placebo and between VIOXX and the nonselective NSAID comparators studied (ibuprofen, diclofenac and nabumetone). The basis for the difference in cardiovascular event rates with VIOXX versus naproxen observed in VIGOR, and the lack of such a difference between VIOXX and placebo or other NSAID comparators in other studies, is not understood. Prospective, well-powered, long-term 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. While low-dose aspirin may be used concomitantly with VIOXX, such concomitant use may result in an increased rate of GI ulceration or other complications compared to use of VIOXX alone. (See CLINICAL STUDIES, Special Studies, Use with Aspirin and Platelets, PRECAUTIONS, Drug Interactions, Aspirin.)

Merck proposes to re-instate previously approved text consistent with labeling for other members of the class.

Merck proposes to delete. Consistent with NSAID class labeling, this information is provided in other parts of the circular. Merck agrees to add pulmonary edema to the ADVERSE REACTIONS section as a post-marketing adverse experience.

Merck proposes this relocation to PRECAUTIONS as in previous VIGOR proposal with revisions as shown.

Merck agrees to bold statement as requested by the Agency and proposes addition of new sentence.

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Hematological Effects

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 PRECAUTIONS, CLINICAL STUDIES, *Special Studies, Platelets*). ~~Thrombocytopenia has been reported in post-marketing in association with VIOXX.~~

Preexisting Asthma

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

Information for Patients

VIOXX can cause discomfort and, rarely, more serious side effects, such as gastrointestinal bleeding, which may result in hospitalization and even fatal outcomes. In a randomized clinical trial, the incidence of serious GI events in patients treated with VIOXX was significantly lower than in patients treated with the comparator NSAID, naproxen. Although serious GI tract ulcerations and bleeding can occur without warning symptoms, patients should be alert for the signs and symptoms of ulcerations and bleeding, and should ask for medical advice when observing any indicative signs or symptoms. Patients should be apprised of the importance of this follow-up (see WARNINGS, *Gastrointestinal (GI) Effects - Risk of GI Ulceration, Bleeding and Perforation*).

Patients should be informed that VIOXX is not a substitute for aspirin for cardiovascular prophylaxis because of its lack of effect on platelets. ~~VIOXX should be used with caution in patients with prior history of hypertension and heart disease.~~

Merck accepts revision to cross-reference.

Merck proposes to delete. Consistent with NSAID class labeling, this information is provided in other parts of the circular.

Merck proposes revisions based upon the VIGOR study.

Merck accepts proposal to re-instate the currently approved text.

Merck proposes to delete for consistency with proposed text in PRECAUTIONS, *Cardiovascular Effects* and for consistency with NSAID class labeling.

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Patients should promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain or edema, ~~chest pain or shortness of breath~~ to their physicians.

Patients should be informed of the warning signs and symptoms of hepatotoxicity (e.g., nausea, fatigue, lethargy, pruritus, jaundice, right upper quadrant tenderness, and "flu-like" symptoms). If these occur, patients should be instructed to stop therapy and seek immediate medical therapy.

Patients should also be instructed to seek immediate emergency help in the case of an anaphylactoid reaction (see WARNINGS).

In late pregnancy VIOXX should be avoided because it may cause premature closure of the ductus arteriosus.

Laboratory Tests

~~Because serious GI tract ulcerations and bleeding can occur without warning symptoms, physicians should monitor for signs or symptoms of GI bleeding.~~

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 mm Hg compared to ACE inhibitor alone. This interaction should be given consideration in patients taking VIOXX concomitantly with ACE inhibitors.

Merck proposes to re-instate the currently approved text.
This text is NSAID class labeling.

Merck proposes to delete based upon the VIGOR study.

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Aspirin: VIOXX can be used concomitantly with low-dose aspirin. 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. 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. (See CLINICAL STUDIES, *Special Studies, Use with Aspirin* and PRECAUTIONS ~~WARNINGS~~, *Cardiovascular Effects*.) ~~No Prospective~~ long-term studies on concomitant administration of VIOXX and aspirin 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_{0-12hr} by 23% and the t_{1/2} by 15%. These small changes are not clinically significant and no dose adjustment is necessary.

Digoxin: Rofecoxib 75 mg once daily for 11 days does not alter the plasma concentration profile or renal elimination of digoxin after a single 0.5 mg oral dose.

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.

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. In post-marketing experience there have been reports of increases in plasma lithium levels. Thus, when VIOXX and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: VIOXX 75 mg administered once daily for 10 days increased plasma concentrations by 23% as measured by AUC_{0-24hr} in patients receiving methotrexate 7.5 to 15 mg/week for rheumatoid arthritis. 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). The effects of the recommended doses for osteoarthritis (12.5 and 25 mg) of VIOXX on plasma methotrexate levels are unknown. Standard monitoring of methotrexate-related toxicity should be continued if VIOXX and methotrexate are administered concomitantly.

Merck proposes to include sentence regarding concomitant use of VIOXX with aspirin. This information has been supplemented with additional clinical trial data provided to the Agency from the ADVANTAGE study. This markedly enhances the experience of patients taking VIOXX concomitantly with aspirin to a level beyond that noted in labeling for other members of the class. Merck believes there are sufficient data to support this claim.

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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: Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing VIOXX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. 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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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 AUC₀₋₂₄) 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 AUC₀₋₂₄) for two years.

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.

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 AUC₀₋₂₄) 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 AUC₀₋₂₄).

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Pregnancy

Teratogenic effects: Pregnancy Category C.

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 AUC₀₋₂₄). 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 AUC₀₋₂₄). There are no studies in pregnant women. VIOXX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic effects: 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 AUC₀₋₂₄ 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 AUC₀₋₂₄). 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 AUC₀₋₂₄). As with other drugs known to inhibit prostaglandin synthesis, use of VIOXX during the third trimester of pregnancy should be avoided.

Labor and delivery

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 AUC₀₋₂₄ at 25 and 50 mg). The effects of VIOXX on labor and delivery in pregnant women are unknown.

Merck & Co., Inc. maintains a registry to monitor the pregnancy outcomes of women exposed to VIOXX while pregnant. Healthcare providers are encouraged to report any prenatal exposure to VIOXX by calling the Pregnancy Registry at (800) 986-8999.

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

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represents an approximate 18- and 6-fold human exposure at 25 and 50 mg based on AUC₀₋₂₄. 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.

Pediatric Use

Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.

Geriatric Use

Of the patients who received VIOXX in osteoarthritis clinical trials, 1455 were 65 years of age or older (this included 460 who were 75 years or older). ~~While no substantial differences in effectiveness were observed between these subjects and younger subjects, as with NSAIDs, elderly patients (over 75 years) or those with a prior history of ulcers or UGI bleeding taking VIOXX have a higher risk for developing a GI bleed than patients with neither of these risk factors (See GI WARNINGS section). Most spontaneous post-marketing reports of fatal GI events have been in the elderly. Most post-marketing reports of acute renal failure have also been in the elderly. 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. Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.~~

In one of these studies (a six-week, double-blind, randomized clinical trial), VIOXX 12.5 or 25 mg once daily was administered to 174 osteoarthritis patients >80 years of age. The safety profile in this elderly population was similar to that of younger patients treated with VIOXX.

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

Merck proposes to re-instate the currently approved text. There are no new data regarding these issues and they are addressed in the WARNINGS, GI Effects and PRECAUTIONS, Renal Effects (as per NSAID class labeling.)

Merck proposes to re-instate currently approved text.

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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				
	Placebo	VIOXX 12.5 or 25 mg daily	Ibuprofen 2400 mg daily	Diclofenac 150 mg daily
	(N = 783)	(N = 2829)	(N = 847)	(N = 498)
<i>Body As A Whole/Site Unspecified</i>				
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
<i>Cardiovascular System</i>				
Hypertension	1.3	3.5	3.0	1.6
<i>Digestive System</i>				
Diarhea	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
<i>Eyes, Ears, Nose, And Throat</i>				
Sinusitis	2.0	2.7	1.8	2.4
<i>Musculoskeletal System</i>				
Back Pain	1.9	2.5	1.4	2.8
<i>Nervous System</i>				
Headache	7.5	4.7	6.1	8.0
<i>Respiratory System</i>				
Bronchitis	0.8	2.0	1.4	3.2

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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, 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, *hepatitis*, intestinal obstruction, *jaundice*, pancreatitis.

Hemic and lymphatic: agranulocytosis, leukopenia, lymphoma, thrombocytopenia.

Immune System: anaphylactoid reaction, angioedema.

Metabolism and Nutrition: hyponatremia.

Nervous System: aseptic meningitis.

Psychiatric: confusion, hallucinations.

Skin and Skin Appendages: severe skin reactions, including Stevens-Johnson syndrome.

Urogenital System: acute renal failure, breast malignant neoplasm, 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.

Merck accepts the addition of pulmonary edema but proposes that it be included as a post-marketing adverse experience, as it is with other NSAIDs, and not as a PRECAUTION as requested by the Agency (see PRECAUTIONS, *Fluid Retention, Edema and Hypertension*.)

Merck proposes to delete. This term will continue to be routinely monitored and reviewed in the next PSUR.

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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.

VIGOR Study

A total of 4047 patients with rheumatoid arthritis were treated with VIOXX 50 mg daily (2 times the maximum dose recommended for chronic use) for a median of 9 months. The general safety profile of VIOXX 50 mg QD in the VIGOR study was similar to that reported for VIOXX 50 mg QD in the OA clinical trials. For specific details on GI and cardiovascular safety see CLINICAL STUDIES, Special Studies, VIGOR and PRECAUTIONS, Cardiovascular Effects.

OVERDOSAGE

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.

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

Merck proposes to retain currently approved text as negotiated with the Agency because it accurately describes the adverse experience profile of VIOXX in this study.

Merck proposes to revise text as shown and add appropriate cross-reference.

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DOSAGE AND ADMINISTRATION

VIOXX is administered orally. The lowest dose of VIOXX should be sought for each patient.

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.

Management of Acute Pain and Treatment of Primary Dysmenorrhea

The recommended initial dose of VIOXX is 50 mg once daily. Subsequent doses should be 50 mg once daily as needed. Use of VIOXX for more than 5 days in management of pain has not been studied (see CLINICAL STUDIES, *Analgesia, including dysmenorrhea*).

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. 3811 — 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.

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No. 3818 — 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

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