



# pharmacists planning service, inc.

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December 7, 2000

*Docket Management*

1031 00 FEB 14 12:53

Janet Woodcock, M.D.  
Director, Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Dear Dr. Woodcock:

We hereby petition the FDA to mandate patient medicine guides (MedGuides) for all prescription drug Cox-II and NSAID preparations. This Petition is submitted pursuant to: a) 21 CFR, Section 10.30; and b) Sections 355 (e) and 314.150 of the Federal Food, Drug and Cosmetic Act.

It has been shown that NSAIDs induce upper GI bleeding which occurs in 5% to 10% of the population who are taking this medication with an estimated 16,500 NSAID-related deaths per year.

The cost of the NSAID-related complications exceeds two billion dollars per year.

As a class, NSAIDs are the most widely used drugs in the United States, with more than seventy million prescriptions written annually.

It has been reported by UK's Committee on Safety of Medicines that over eleven deaths have been associated with the use of Rofecoxib (Vioxx) during the drug's first year on the market in the UK.

I am sending along a copy of the November, 2000 "Worst Pills/Best Pills News" in which it states adverse GI reactions from upper GI perforations, ulcerations and bleeding occur especially in the over-65 years of age.

I have written the enclosed letter to Mr. Raymond Gilmartin, President/CEO, Merck outlining PPSI's concerns.

*00P-1671*

*CP 1*

We respectfully request FDA initiate these MedGuides on all NSAIDs and Cox-II drugs.

The longer the delay in educating patients, the larger the toll of preventable GI bleeds and other serious damage to the public.

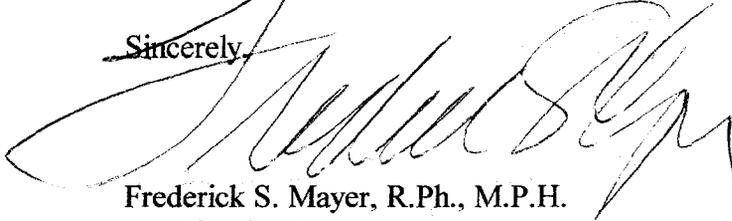
#### ENVIRONMENTAL IMPACT STATEMENT

Nothing requested in this Petition will have an impact on the environment.

#### CERTIFICATION

We certify that, to the best of our knowledge and belief, this Petition includes all information and views on which this Petition relies and that includes representative data and information known to the petitioners which are unfavorable to the Petition.

Sincerely,

A large, stylized handwritten signature in black ink, appearing to read 'Frederick S. Mayer', is written over the word 'Sincerely'.

Frederick S. Mayer, R.Ph., M.P.H.  
President/CEO  
Pharmacists Planning Service, Inc. (PPSI)



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December 7, 2000

Raymond V. Gilmartin, President/CEO  
Merck and Company, Inc.  
One Merck Drive, POB 100  
Whitehouse Station, New Jersey 08889-4044

Dear Mr. Gilmartin:

I am writing this letter to you regarding concerns of Pharmacists Planning Service, Inc. (PPSI), a 501 C (3) non-profit public health, consumer, pharmacy education organization, regarding the Committee on Safety of Medicines' (the United Kingdom's (UK) equivalent to our US Food and Drug Administration (FDA)), most recent report in the September, 2000, issue of "Current Problems in Pharmacovigilance".

Our major concerns are regarding Merck's prescription drug, Vioxx (Rofecoxib), which is being used for the treatment of both osteoarthritis and acute pain in adults. To summarize the concerns from June, 1999 and up to July, 2000, a total of 1,120 reports of suspected adverse reactions have been received by the Committee on Safety of Medicines.

Adverse GI reactions accounted for almost half of all reports of these. Most were nausea, upset stomach, diarrhea and abdominal pain. More serious were 68 reports or 12% of patients reporting of upper GI perforations, ulcerations and bleeding (PUBs). In patients with PUBs, five died.

In this same report 177 reports of suspected cardiovascular adverse reactions with swelling, high blood pressure and palpitations were recorded.

There were 15 reports of heart failure, of aggravated heart failure. Of these 15 reports, **THREE PATIENTS DIED.**

There were 9 reports of heart attacks—**THREE FATAL.**

Various psychiatric reactions were reported with Rofecoxib (Vioxx) use--depression, confusion, hallucinations. The majority of the patients were reported to have recovered

after Rofecoxib was stopped. Other adverse drug reactions were reported with this drug including hives, bronchospasms and worsening of asthma along with 65 cases reported of kidney failure, 12 reports of abnormal liver function and serious skin rashes. Altogether there were 11 reports of death associated during the first year of marketing this drug in the United Kingdom.

PPSI's major concern is that in Merck's full page ads to both healthcare professionals and consumers in the direct-to-consumer advertising (DTCA) Merck is saying "Once daily power for STRENGTH, SAFETY AND ONCE DAILY POWER".

In the AMA "Archives of Internal Medicine", June 24, 2000 article by Ric Day, M.D., et al. entitled "A Randomized Trial of the Efficacy and Tolerability of the Cox-II Inhibitor Rofecoxib vs. Ibuprofen in Patients with Osteoporosis" it states in the conclusion "Rofecoxib was well tolerated and provided clinical efficacy comparable with a high dose of the NSAID Ibuprofen".

Since it has been reported that the mortality of patients hospitalized with NSAID-induced upper GI bleeding is 5% to 10%, with an estimated 16,500 NSAID-related deaths per year with the cost of NSAID-related GI complications exceeding two million per year - how safe is your Rofecoxib product in light of the UK study?

In the "Dear Doctor" letter from Merck signed by Gail A. Ryan, Professional Services, which quotes a paper from "Arthritis and Rheumatism", Volume 43, Number 5, May, 2000, printed by the American College of Rheumatology, by Grant W. Canon, M.D., et al. entitled "Rofecoxib, a Specific Inhibitor of Cyclooxygenase 2, with Clinical Efficacy Comparable with That of Diclofenac Sodium", it states on Page 983 "The difference in incidents of GI adverse events (comparing Rofecoxib with Diclofenac Sodium) were comparable". IF THIS BE THE CASE AND WE KNOW OF THE NSAID INDUCED GI BLEEDS AND THE 16,500 RELATED DEATHS PER YEAR, WHY IS MERCK CONTINUING TO SAY THAT VIOXX IS SAFE ESPECIALLY AFTER THESE COMPARISONS?

PPSI respectfully requests:

1. Merck put out a patient package consumer information medicine guide at its earliest convenience for Vioxx for each prescription dispensed by healthcare professionals.
2. In light of the UK report that an education and awareness campaign be instituted ASAP to educate healthcare professionals about the increased reports of death associated with the use of Rofecoxib.
3. That in all full page direct-to-consumer ads (DTCA) the word "safety" be deleted and adequate warnings be given to consumers IN BOLD LETTERS on the adverse risk reactions which can result in this issue.

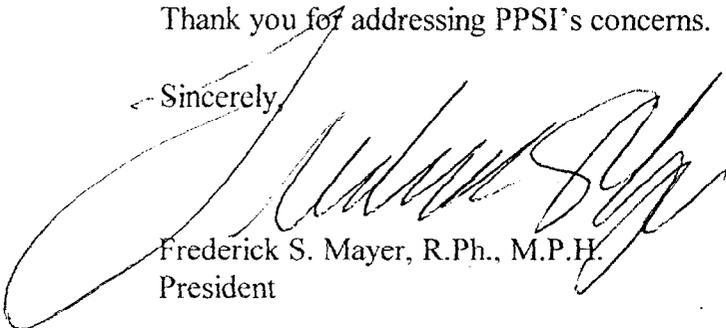
4. That Rofecoxib is widely assumed (without definitive evidence) to be a much safer NSAID for the gastrointestinal (GI) tract than the other drugs in its class because it works by a new mechanism of action. One of PPSI's concerns is that since this drug works in a new way, it may also cause harm in a new way. We would like this reported in a fair and balanced manner.

Finally, I would like to ask for more data and information on the safety and efficacy of this product in lieu of the reported deaths in the UK.

How many deaths have been reported in the United States? If 11 deaths have been reported in England in one year, is it safe to say that since England has a population of 60 million, there would be at least 55 deaths reported in the US from use of this drug?

Thank you for addressing PPSI's concerns.

Sincerely,



Frederick S. Mayer, R.Ph., M.P.H.  
President

# Update from the United Kingdom on Adverse Drug Reactions Reported for the Arthritis Drug Rofecoxib (VIOXX)

The Committee on Safety of Medicines, the United Kingdom's (U.K.) equivalent to our Food and Drug Administration (FDA), summarized the adverse reactions they had received for the new osteoarthritis drug rofecoxib (VIOXX) during its first year of marketing in the September 2000 issue of *Current Problems in Pharmacovigilance*.

We reviewed rofecoxib in the July 1999 issue of *Worst Pills, Best Pills News* and recommended that it not be used before July 2004 because it did not offer any documented advantage in effectiveness or safety over the more than 20 nonsteroidal anti-inflammatory drugs (NSAIDs) currently on the market in the U.S. Rofecoxib is widely assumed (without definitive evidence) to be a much safer NSAID for the gastrointestinal (GI) tract than the other drugs in its class because it works by a new mechanism of action. One of our concerns is that a drug that works in a new way may also cause harm in a new way.

Rofecoxib was first marketed in Britain in June 1999 and up through July 2000 a total of 1,120 reports of suspected adverse reactions had been received by the Committee on Safety

of Medicines. It was estimated that 557,100 prescriptions had been dispensed for the drug up to the end of May 2000.

Adverse GI reactions accounted for almost half (554) of all reports. Of these, most (84 percent) were nausea, upset stomach, diarrhea and abdominal pain. More serious were 68 reports (12 percent) of upper GI perforations, ulceration and bleeding. Perforations, ulceration and bleeding go by the acronym PUBs. In patients with PUBs, 44 (65 percent) recovered, but five died. More than two thirds (69 percent) of the patients experiencing PUBs were over 65 years of age. In six cases, aspirin or another NSAID was also implicated, and another 10 patients were taking aspirin at the same time as rofecoxib.

There were 177 reports of suspected cardiovascular adverse reactions. Most of these were of swelling (101 reports), high blood pressure (31) and palpitations (19). There were 15 reports of heart failure, or aggravated heart failure. Of these 15 reports, three patients died.

There were also nine reports of heart attack, three fatal. In most of these cases, the patient had risk factors for cardiovascular disease.

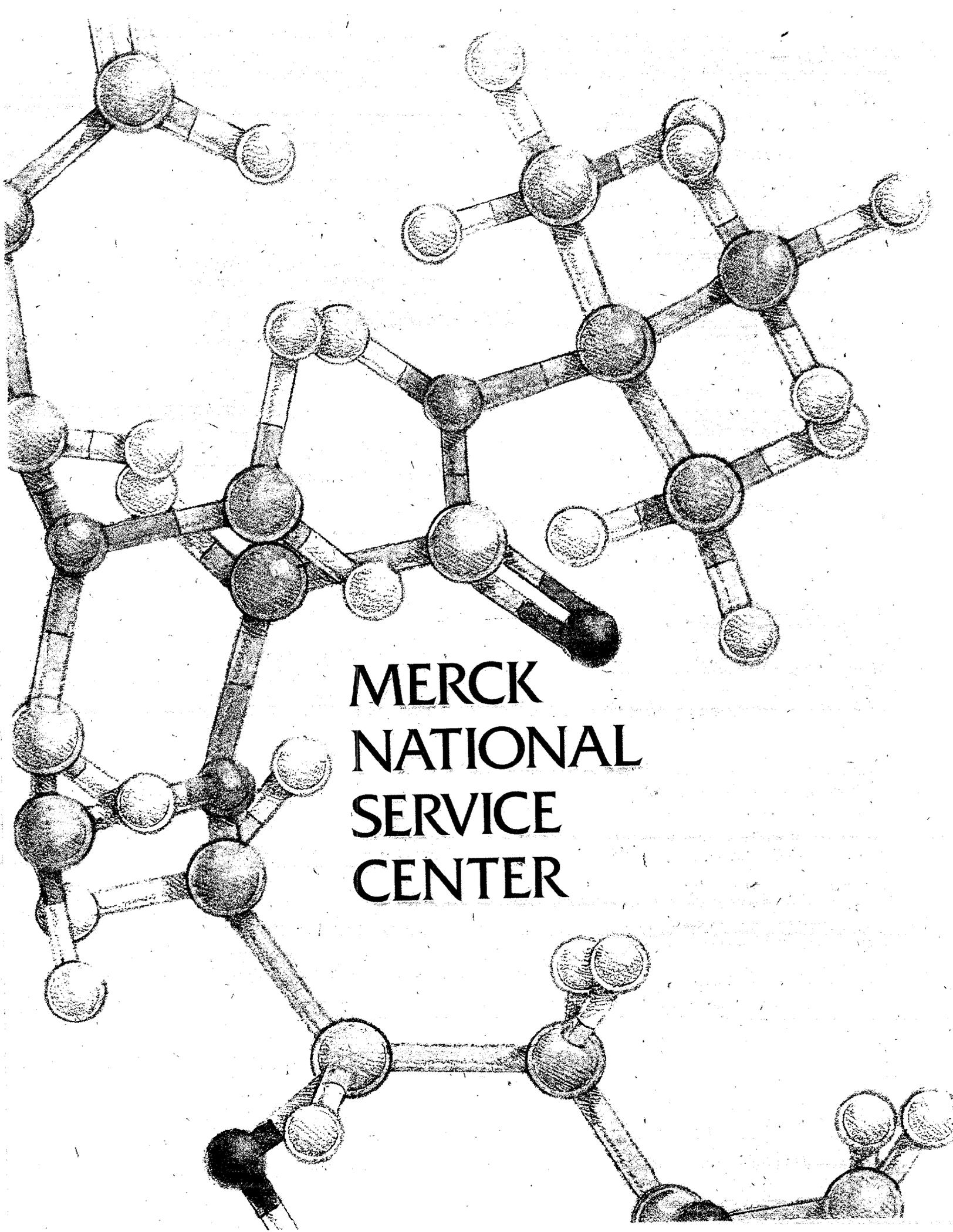
Various psychiatric reactions were reported with rofecoxib use. These included depression (28 reports), confusion (14 reports) and hallucinations (11 reports). The majority of patients were reported to have recovered after rofecoxib was stopped.

Adverse drug reactions that are known to occur with other NSAIDs were also reported with rofecoxib. These included hives (35 reports), bronchospasm or worsening of asthma (25 reports), kidney failure (16 reports), abnormal liver function (12 reports), and serious skin rashes (3 reports).

Altogether there have been 11 reports of death associated with the use of rofecoxib during the drug's first year on the market in the U.K.

## What You Can Do

You should wait at least until July 2004 to take rofecoxib unless compelling research is presented to the FDA that allows a change in the drug's professional product labeling or "package insert" stating that this drug is safer or more effective than the numerous other older NSAIDs now on the market.



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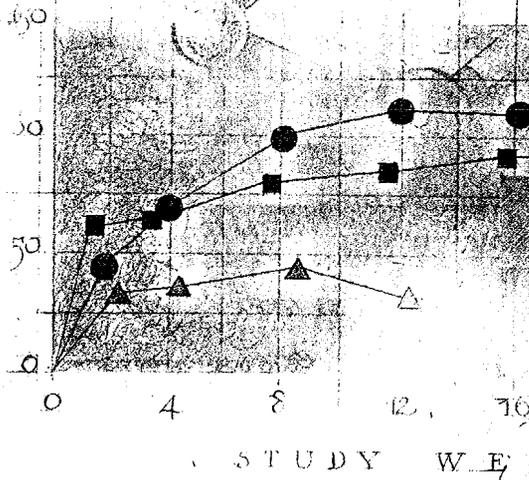
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MEAN CHANGE FROM BASELINE



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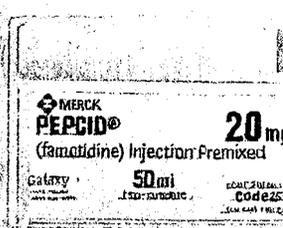
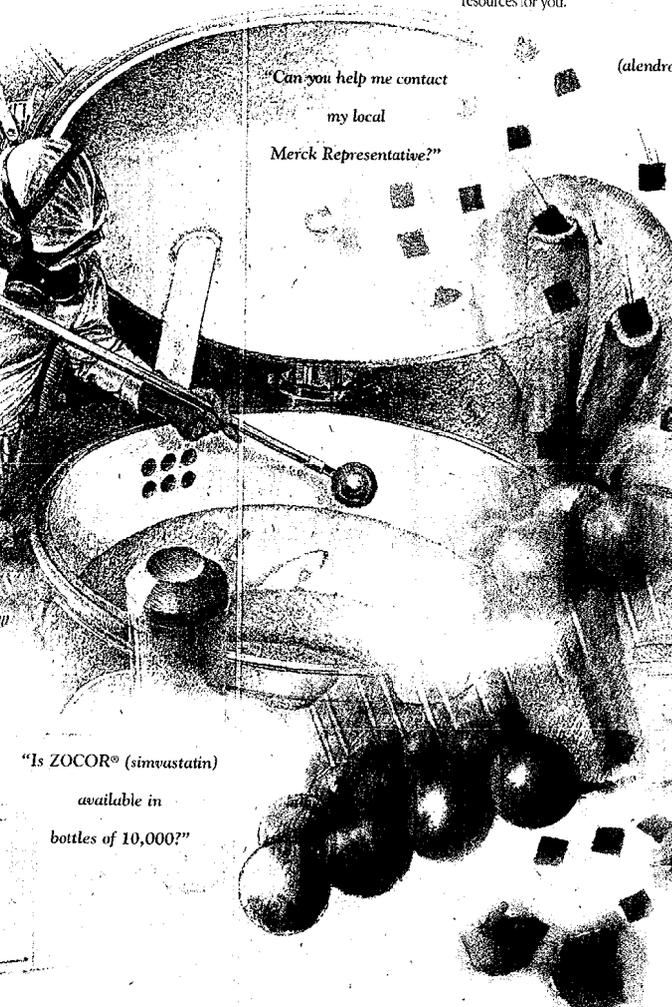
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# ARCHIVES

OF

# INTERNAL MEDICINE

June 26, 2000

## A Randomized Trial of the Efficacy and Tolerability of the COX-2 Inhibitor Rofecoxib vs Ibuprofen in Patients With Osteoarthritis

*R. Day, B. Morrison, A. Luza, O. Castaneda,  
A. Strusberg, M. Nahir, K. B. Helgetveit,  
B. Kress, B. Daniels, J. Bolognese,  
D. Krupa, B. Seidenberg, E. Ehrich,  
for the Rofecoxib/Ibuprofen Comparator Study Group*

American Medical Association

Physicians dedicated to the health of America



**REPRINT**

R-VIO-2610(1)-0700



Dear Doctor:

Thank you for your interest in this reprint, "A Randomized Trial of the Efficacy and Tolerability of the COX-2 Inhibitor Rofecoxib vs Ibuprofen in Patients With Osteoarthritis," by Ric Day et al, published in *Archives of Internal Medicine*, Volume 160, June 2000. We are pleased to provide this article to you as requested.

This study, a randomized, double-blind trial in 809 adults in whom the knee or hip was the primary source of pain, compared the clinical efficacy and tolerability of VIOXX<sup>®</sup> (rofecoxib) with that of ibuprofen.

Patients were randomized to one of four treatment groups: placebo; 12.5-mg VIOXX once daily; 25-mg VIOXX once daily; or 800-mg ibuprofen three times a day. Clinical efficacy and safety were monitored during a six-week treatment period.

VIOXX is indicated for relief of the signs and symptoms of osteoarthritis, the management of acute pain in adults (see CLINICAL STUDIES), and the treatment of primary dysmenorrhea.

**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 other allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

VIOXX is **not** a sulfonamide; therefore, VIOXX has **no** sulfonamide contraindication.

Serious gastrointestinal toxicity can occur with or without warning symptoms with NSAIDs.

Before prescribing VIOXX, please read the accompanying complete Prescribing Information. Thank you for your interest in this information about VIOXX.

Very truly yours,

A handwritten signature in black ink that reads "Gail A. Ryan".

Gail A. Ryan  
Professional Services

Enclosure: Prescribing Information for VIOXX

VIOXX is a registered trademark of Merck & Co., Inc.

R-VIO-2610(1)-0700

# A Randomized Trial of the Efficacy and Tolerability of the COX-2 Inhibitor Rofecoxib vs Ibuprofen in Patients With Osteoarthritis

Ric Day, MD; Briggs Morrison, MD; Armando Luza, MD; Oswaldo Castaneda, MD; Alberto Strusberg, MD; Menachem Nahir, MD; Knut Bjorn Helgetveit, MD; Barbara Kress, RN; Brian Daniels, MD; James Bolognese; Dave Krupa; Beth Seidenberg, MD; Elliot Ehrich, MD; for the Rofecoxib/Ibuprofen Comparator Study Group

**Background:** Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). It is not known whether a specific inhibitor of COX-2 will provide efficacy in osteoarthritis (OA) comparable with NSAIDs. Therefore, we compared the efficacy and safety of the rofecoxib, which specifically inhibits COX-2, with those of the NSAID ibuprofen in patients with OA.

**Objective:** To compare the clinical efficacy and tolerability of rofecoxib (12.5 and 25 mg once daily) with ibuprofen (800 mg 3 times daily).

**Methods:** A randomized, double-blind trial of 809 adults with OA was conducted. Patients with OA in whom the knee or hip was the primary source of pain were randomized to 1 of 4 treatment groups on demonstration of disease activity: placebo; rofecoxib, 12.5 or 25 mg once daily; or ibuprofen, 800 mg 3 times daily. Clinical efficacy and safety were monitored during a 6-week treatment period.

**Results:** Both doses of rofecoxib demonstrated efficacy clinically comparable with ibuprofen as assessed by 3 primary end points (pain walking on a flat surface [Western Ontario and McMaster Universities Osteoarthritis Index], patient global assessment of response to therapy, and investigator global assessment of disease status) according to predefined comparability criteria. Both rofecoxib doses and the ibuprofen dose provided significantly ( $P < .001$ ) greater efficacy than placebo on all primary end points. Results from secondary end points were consistent with those of the primary end points. All treatments were well tolerated; the overall incidence rates of clinical adverse experiences were not significantly different ( $P > .05$ ) among the treatment groups.

**Conclusion:** Rofecoxib was well tolerated and provided clinical efficacy comparable with a high dose of the NSAID ibuprofen.

*Arch Intern Med.* 2000;160:1781-1787

From St Vincent's Hospital, Darlinghurst, Australia (Dr Day); Merck Research Laboratories, Rahway, NJ (Drs Morrison, Daniels, Seidenberg, and Ehrich, Ms Kress, and Msrs Bolognese and Krupa); Clinica San Pablo, Surca Lima, Peru (Dr Luza); Clinica Anglo-Americana, Lima, Peru (Dr Castaneda); Department of Rheumatology, Rambam Medical Center, Haifa, Israel (Dr Nahir); and Martina Hansens Hospital, Baerum, Norway (Dr Helgetveit). Dr Strusberg is in private practice in Cordoba, Argentina. See the acknowledgments for a list of the other members of the Rofecoxib/Ibuprofen Comparator Study Group.

**N**ONSTEROIDAL anti-inflammatory drugs (NSAIDs) are commonly used to treat the pain and inflammation caused by a variety of clinical disorders, including osteoarthritis (OA). The clinical effects of these drugs result primarily from the inhibition of the enzyme cyclooxygenase (COX), the first step in the conversion of arachidonic acid to prostaglandins.<sup>1</sup>

Two COX isoforms (COX-1 and COX-2) have been identified and characterized.<sup>2,5</sup> Cyclooxygenase-1 is constitutively active throughout the body<sup>6,7</sup> and is only slightly upregulated in some cells in response to hormones or growth factors.<sup>8,9</sup> In contrast, under basal conditions, COX-2 expression is restricted to the brain,<sup>10,11</sup> reproductive tract,<sup>12</sup> kidney,<sup>13</sup> and pancreatic islet cells,<sup>14</sup> but it is markedly upregulated in response to inflam-

mation and other stressors.<sup>15-20</sup> These distinct expression patterns have led to the proposal that prostaglandins produced by COX-1 are largely responsible for physiologic functions,<sup>21</sup> while COX-2-derived prostaglandins mediate pathophysiologic and inflammatory processes.<sup>21</sup>

In vitro and ex vivo assays have shown that NSAIDs nonspecifically inhibit both the COX-1 and COX-2 isoforms.<sup>21-25</sup> As prostaglandins are involved in the maintenance of gastrointestinal (GI) tract mucosal integrity, the well-recognized toxic effects of NSAIDs on the GI tract<sup>26</sup> have been proposed to result largely from inhibition of COX-1 activity.<sup>21,27</sup> The therapeutic effects of NSAIDs may be attributable to COX-2 inhibition.<sup>21,28,29</sup> Therefore, agents that specifically inhibit COX-2 are being evaluated to determine whether they have efficacy equal to NSAIDs with an improved GI tract safety profile.

## METHODS

The primary objective of this randomized, placebo-controlled clinical trial was to compare the clinical efficacy of rofecoxib (12.5 and 25 mg once daily) with ibuprofen (800 mg 3 times daily). All subjects gave written informed consent. The study protocol was approved by the institutional review boards or ethical review committees for all 49 investigative sites in 26 countries.

### STUDY DESIGN

On confirmation of eligibility, patients were randomized to 1 of 4 treatment groups by a computer-generated allocation schedule: placebo, rofecoxib, 12.5 or 25 mg once daily, or ibuprofen, 800 mg 3 times daily. The primary purpose of this study was to compare the efficacy of rofecoxib with that of ibuprofen; a smaller placebo group was included to confirm that rofecoxib and ibuprofen had efficacy greater than that of the placebo. Thus, the allocation was 1:4:4:4 for placebo, both doses of rofecoxib, and ibuprofen. The masked allocation schedule was generated by an individual not otherwise involved with the study and kept concealed from all study participants. The allocation schedule was unblinded once all data had been entered, reviewed, and certified. Medication was provided in blister packages; study blinding was maintained by using a matching placebo for each study medication. Patients took 3 tablets each morning and 1 tablet at both midday and evening. Patients returned approximately every 2 weeks for 3 visits to assess both efficacy and safety. Patients were provided open-label acetaminophen for osteoarthritic pain not adequately controlled by the study medication; the maximum daily dose of acetaminophen allowed was 2600 mg, and the amount used was recorded. Patients returned 7 to 10 days after their last dose of study medication for posttherapy safety assessment.

### ENTRY CRITERIA

The study included 2 groups of patients with OA. NSAID users: These patients discontinued their prior NSAID therapy on confirmation of eligibility. Following a washout period (longer than 5 plasma half-lives of prior NSAID use), patients' pain walking on a flat surface was assessed using question 1 of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC 3.0),<sup>33</sup> a patient-reported 100-mm visual analog scale (VAS). Patients were randomized to the study if they reported a minimum of 40 mm and an increase of 15 mm on the VAS compared with the value at the screening visit (ie, before discontinuation of NSAIDs), and if the investigator's global assessment of disease status worsened by at least 1 point on a 0-to-4 Likert scale compared with the screening visit.

Acetaminophen users: Patients who used acetaminophen instead of NSAIDs for the treatment of OA were randomized if at both the screening and randomization visits they met all 3 of the following criteria: (1) they reported a minimum of 40 mm on the pain VAS (question 1 of the WOMAC), (2) they reported a minimum of 40 mm on a separate VAS evaluating the patient's global assessment of disease status, and (3) the investigator rated the global assessment of disease status as fair, poor, or very poor.

The diagnosis of OA was based upon clinical and radiographic evidence of OA (joint space narrowing and osteophytes for knee and joint space narrowing for hip). Other entry criteria included age 40 years or older, American Rheumatism Association (ARA; Steinbrocker system) functional class I, II, or III<sup>34</sup>; symptomatic for at least 6 months; the knee or hip the primary source of pain or disability; and, for women, postmenopausal or demonstrably non-gravid. Patients were excluded if they had significant renal impairment (estimated creatinine clearance  $\leq 0.50$  mL/s [ $\leq 30$  mL/min] or serum creatinine level  $>177$   $\mu\text{mol/L}$  [ $>2.0$  mg/dL]), clinically significant abnormal results of physical examination or laboratory screening, a positive fecal occult blood test result, malabsorption, class III/IV angina or congestive heart failure, uncontrolled hypertension, stroke or transient ischemic attack within 2 years, active hepatic disease, a history of recent neoplastic disease, or an allergy to acetaminophen or NSAIDs. Patients were excluded if they required aspirin at any dose, corticosteroids, warfarin sodium, or ticlopidine hydrochloride.

### EFFICACY ASSESSMENTS

To obtain a comprehensive assessment of the effect of rofecoxib on the multiple clinical manifestations of OA, a variety of efficacy end points were included in the study that were derived from the assessments made by both the patient and the investigator.

At each visit, the patient completed the WOMAC<sup>33</sup> and a global assessment of overall disease status (100-mm VAS, ranging from "very well" to "very poor"). At treatment visits, the patient also rated the overall response of his or her OA to study medication on a 0-to-4 Likert scale ("none" to "excellent"). The physician rated (1) overall assessments of disease status (0-to-4 Likert scale of "very poor" to "very well"), (2) overall response of the patient's OA to study medication, and (3) study joint tenderness. Examination of study knee or hip joint for tenderness was performed with the patient in the supine position. Tenderness was defined as pain in response to passive motion or pressure; the hip was internally and externally rotated, and the knee was moved through the full available range to detect any end range pain and palpated around the medial and lateral joint lines while the knee was in the neutral position. Pain on palpation (knee only) or during passive range

Rofecoxib, 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone, inhibits human COX-2 with a greater than 800-fold degree of selectivity relative to COX-1 in an in vitro assay with Chinese hamster ovary cell lines expressing COX-1 or COX-2.<sup>30</sup> Using ex vivo human whole blood assays, rofecoxib showed dose-related inhibition of COX-2 activity but no significant inhibition of COX-1 activity with single oral doses ranging from 5

to 1000 mg.<sup>30</sup> Rofecoxib is, therefore, a specific inhibitor of the COX-2 isoform in humans.

Clinical evidence to support the hypothesis that rofecoxib has an improved GI tract safety profile compared with NSAIDs would consist of data demonstrating that rofecoxib provides improved GI tract safety compared with an NSAID at doses that provide comparable clinical efficacy. In 2 large multicenter

of motion (hip and knee) was graded according to the following scale: 0, no pain; 1, patient states there is pain; 2, patient states there is pain and winces; and 3, patient states there is pain, winces, and withdraws.

Other measurements of efficacy included amount of rescue acetaminophen consumed and discontinuation from the study because of lack of efficacy of the study medication. The primary end points were pain walking on a flat surface, patient response to therapy, and investigator global assessment of disease status. Secondary end points included the WOMAC subscales (pain, stiffness, and disability), patient global assessment of disease status, investigator assessment of response to therapy, patients discontinued from the study because of lack of efficacy, acetaminophen use, and study joint tenderness.

#### TOLERABILITY ASSESSMENTS

Spontaneously reported adverse experiences and vital signs were monitored at every visit. Laboratory investigations, including hematology (complete blood cell count with differential), chemistry (electrolyte, urea nitrogen, creatinine, total protein, albumin, calcium, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, and total bilirubin levels), and urinalysis (protein, glucose, pH, red blood cells, and white blood cells, with microscopic examination if there were any abnormal results) were performed at screening, randomization, 4 and 6 weeks of therapy, and the posttherapy visit. For all adverse experiences, the investigator recorded the intensity, the relation to test drug ("definitely not" and "probably not" related were scored as not drug-related adverse experiences; "possibly," "probably," and "definitely" related were scored as drug-related adverse experiences), the outcome, and any action taken.

#### STATISTICAL ANALYSIS

The primary measure for each efficacy end point (except discontinuation because of lack of efficacy) was the mean response (change from baseline) over all observation times in the 6-week treatment period. All data collected from discontinuation and unscheduled visits were included in this analysis; no missing values were imputed. For each end point, a patient had to have a baseline measurement and at least 1 measurement during the 6-week treatment period for the mean change from baseline to be computed. Only 14 of the 809 randomized patients were excluded from the analysis for one or more of the primary end points because of missing baseline or on-treatment data. Eighty-five percent of the randomized patients had a measurement recorded for all 3 primary end points at all of the planned observation times.

For each end point, analysis of covariance (ANCOVA) was used to model patient mean change from baseline

as a function of the categorical predictors treatment, study center, and history of ulcer or upper GI tract bleeding, and a continuous covariate, the baseline measurement. Mean patient change from baseline and SEs resulting from the ANCOVA were used to compute 95% confidence intervals (CIs) for the between-treatment difference in mean response, tests to compare mean response with active treatments against the placebo, and posterior probabilities (based on Bayesian analyses with noninformative prior distributions<sup>35</sup>) that the true mean differences in response to the active treatments were within the predefined clinical comparability bounds. All statistical tests for difference were 2-tailed with  $P = .05$ ;  $P \leq .05$  was considered statistically significant.

The primary hypothesis of this study was that rofecoxib would provide clinical efficacy comparable with ibuprofen as assessed by 3 primary end points: pain walking on a flat surface, patient response to therapy, and investigator global assessment of disease status. The following conditions had to be satisfied to conclude that the treatments were clinically comparable: in any 2 of the 3 primary end points, the 95% CIs of mean differences between treatment groups had to be within predefined comparability bounds ( $\pm 10$  mm on a 100-mm VAS and  $\pm 0.5$  on a Likert scale), and all of the 3 posterior probabilities were required to be 0.950 or lower. These clinical comparability bounds are more conservative than those proposed by a consensus panel of rheumatologists<sup>36</sup> and were derived from results of previous OA trials with rofecoxib.

Separate analyses were performed to evaluate effects on treatment differences of subgroup factors, including race, age, sex, study joint (knee vs hip), and prior OA medication use (NSAID vs acetaminophen). These were assessed individually by adding each subgroup factor and its interaction with treatment to the ANCOVA model for each of the 3 primary end points.

Safety was assessed by comparing incidence rates of adverse experiences and exceeding predefined limits of change in laboratory and vital sign variables between the treatment groups. These between-group comparisons were calculated using the Fisher exact test; a step-down approach (25 mg first, and if significant, followed by 12.5 mg) was used for the comparisons of rofecoxib doses vs placebo.

This study had greater than 99% power to demonstrate comparable efficacy (according to the criteria cited) between rofecoxib and ibuprofen if their true difference is 0. Power calculations were based on observed treatment effects in other placebo-controlled studies with rofecoxib. Since this study was designed using variability data from a pilot study (data on file, Merck Research Laboratories), provision was made for larger variability. If the underlying SDs were 25% larger than those observed in the pilot study, the power was approximately 94%.

endoscopy studies<sup>31,32</sup> performed in patients with OA, rofecoxib, 25 mg taken once daily, caused fewer endoscopically detected gastroduodenal ulcers than ibuprofen, 2400 mg (800 mg 3 times daily). Therefore, we undertook a prospective randomized study with the hypothesis that rofecoxib, 25 mg, would provide comparable clinical efficacy with ibuprofen, 800 mg 3 times daily. The main outcome measures were patient

and physician assessments of efficacy in the treatment of OA.

## RESULTS

Between April 30 and November 7, 1997, 1023 patients with OA were screened and 809 were enrolled in the study (**Figure 1**). Patients randomly assigned to the 4 treat-

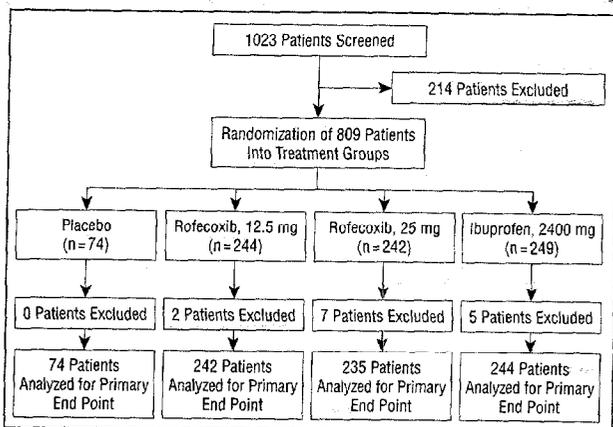


Figure 1. Randomized trial profile.

ment groups had similar sociodemographic and clinical characteristics, including baseline values for efficacy end points (Table 1, Figure 1, and Figure 2; additional data not shown).

Of the 809 patients, 709 (88%) completed the study; the overall discontinuation rate was comparable among treatment groups (Figure 3; additional data not shown). There was a significantly higher discontinuation rate because of clinical adverse experiences in the ibuprofen group compared with the placebo group ( $P < .05$ ), whereas both rofecoxib groups were not significantly different from placebo. There were significantly fewer discontinuations because of lack of efficacy ( $P \leq .009$ ) in the active therapy groups compared with the placebo group (Figure 3). The number of patients who withdrew for other reasons was similar between all groups ( $P > .05$ ).

## EFFICACY

Figure 2 presents the mean change from baseline during the 6-week treatment period for the 3 primary end points (pain walking on a flat surface, patient response to therapy, and investigator global assessment of disease status) and the secondary end point of the physical function subscale of the WOMAC; data for all primary and secondary end points are shown in Table 2. For all 4 end points, the treatment effect was similar among all active groups and was superior to the placebo group. Maximum treatment effects were seen (Figure 2) by the first evaluation (2 weeks) and were sustained throughout the 6-week treatment period. The treatment effect of rofecoxib was consistently seen for all primary and secondary end points (Figure 2 and Table 2); for each end point the effect was similar among all active groups, and all active groups were superior to the placebo group.

The clinical efficacy of both rofecoxib doses was comparable with that of ibuprofen during 6 weeks of treatment using the prespecified comparability criteria (see the "Methods" section). For all 3 primary end points, the 95% CIs for the difference of mean response between each of the treatment pairs (rofecoxib, 25 mg, and ibuprofen; rofecoxib, 12.5 mg, and ibuprofen; and rofecoxib, 25-12.5 mg, and ibuprofen) were within the predefined comparability bounds, and the posterior probability that the true mean difference was within the predefined com-

Table 1. Patient Characteristics by Treatment Assignment\*

	Placebo (n = 74)	Rofecoxib, 12.5 mg (n = 244)	Rofecoxib, 25 mg (n = 242)	Ibuprofen, 2400 mg (n = 249)
Age, y, mean $\pm$ SD	63.1 $\pm$ 9.7	64.9 $\pm$ 8.4	62.8 $\pm$ 9.3	64.1 $\pm$ 8.3
Female, %	85.1	81.1	78.9	78.3
Duration of osteoarthritis, y, mean $\pm$ SD	9.3 $\pm$ 8.4	8.3 $\pm$ 6.4	8.5 $\pm$ 7.1	9.0 $\pm$ 7.5
ARA functional class II or III, %	88	88	86	85
Knee/hip as study joint, %	77/23	78/22	80/20	75/25
Prior use of NSAIDs, %	91	91	87	92

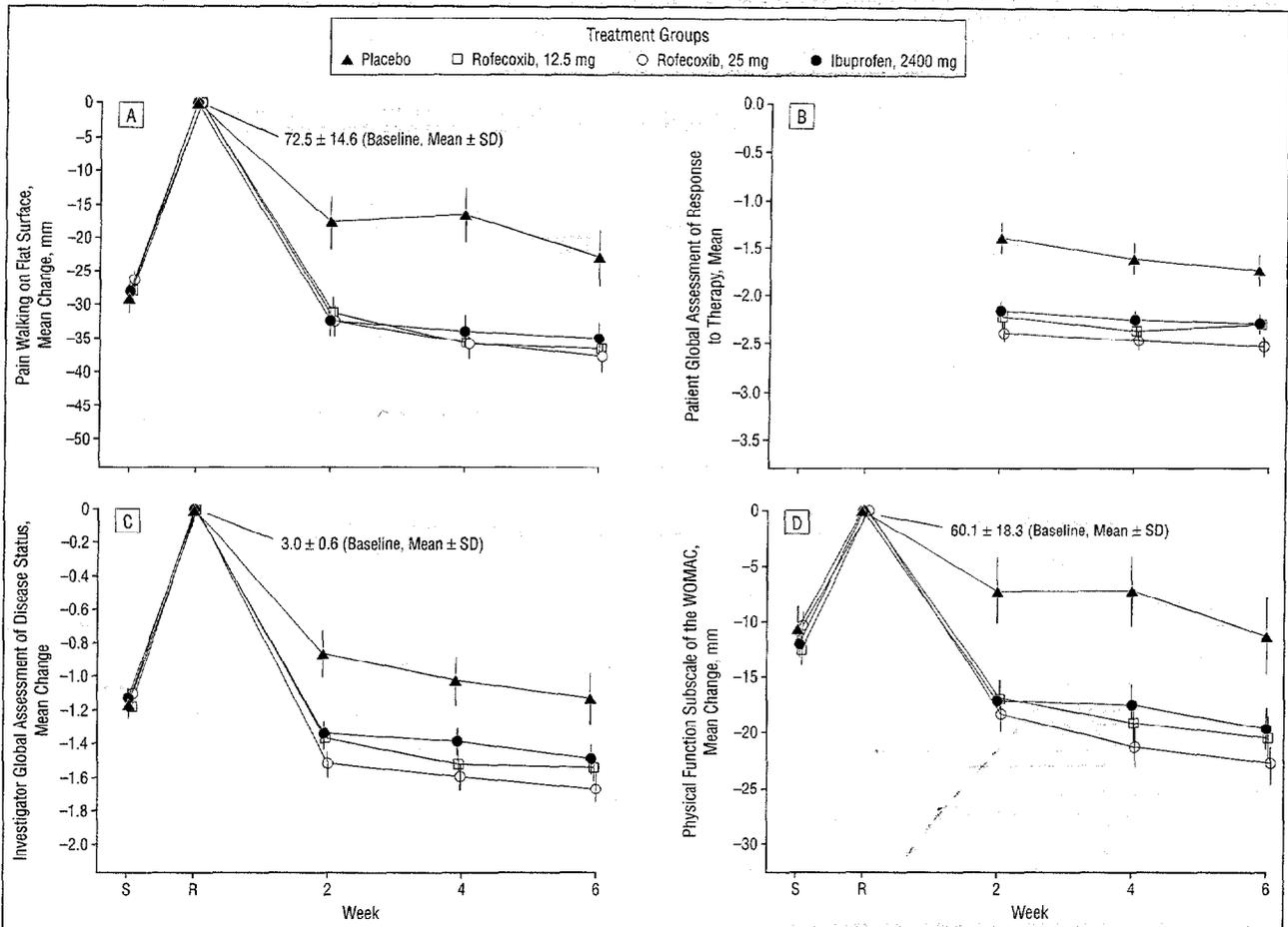
\*ARA indicates American Rheumatism Association; NSAIDs, nonsteroidal anti-inflammatory drugs.

parability bounds was greater than 0.950. The effect of rofecoxib, 25 mg, was significantly superior to that of ibuprofen ( $P < .05$ ) for 2 of the 3 primary end points (patient response to therapy [ $P = .005$ ] and investigator global assessment of disease status [ $P = .005$ ]).

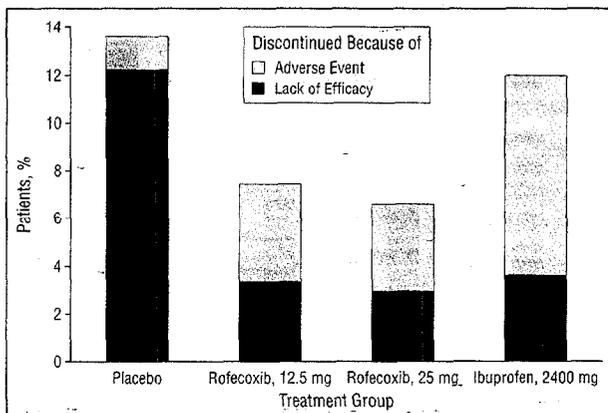
Analyses were performed to determine if the treatment effects observed were consistent across various subgroups of patients using treatment-by-subgroup analyses for the 3 primary end points. Treatment effects were consistently observed whether the patients had knee vs hip as the primary study joint and whether they were an acetaminophen user vs an NSAID user at study entry. No statistically significant interactions were observed between treatment and study center, sex, race, age, or ARA functional class at study entry.

## TOLERABILITY

The incidence of any clinical adverse event was not significantly different among the treatment groups (41.9% in the placebo group vs 50.8% [rofecoxib, 12.5 mg], 53.3% [rofecoxib, 25 mg], and 51.8% [ibuprofen] in the active groups). Drug-related clinical adverse events were more common in all active therapy groups compared with placebo (10.8% vs 27.5%, 31.0%, and 30.5%, respectively;  $P = .003$ ). Clinical adverse events that led to discontinuation from the study were most common in the ibuprofen group (1.4% vs 4.1%, 3.7%, and 8.4%, respectively;  $P = .03$  vs placebo for ibuprofen only); this was mostly accounted for by adverse experiences related to the GI tract. Two symptomatic gastric ulcers were observed in the study; both were in the ibuprofen treatment group. The most common clinical adverse experiences were epigastric discomfort (0% vs 5.7%, 5.8%, and 8.0%, respectively), diarrhea (4.1% vs 4.5%, 5.0%, and 5.2%, respectively), and nausea (1.4% vs 2.9%, 6.6%, and 3.6%, respectively). The incidence of any laboratory adverse event was not significantly different among the treatment groups (4.1% in the placebo group vs 10.7% [rofecoxib, 12.5 mg], 7.6% [rofecoxib, 25 mg], and 13.4% [ibuprofen] in the active groups). The mean changes in body weight and blood pressure were similar in all treatment groups. Adverse experiences of edema or hyper-



**Figure 2.** Treatment effects over time for the 3 primary clinical efficacy end points. S indicates screening visit; R, randomization visit; and WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index. Error bars indicate 84% confidence intervals. All active treatments were superior to placebo ( $P < .001$ ).



**Figure 3.** Patients discontinued from the study because of lack of efficacy or adverse experience. The rate of discontinuation for lack of efficacy was greater in the placebo group compared with each of the treatment groups ( $P < .05$ ). The rate of discontinuation for an adverse event was greater only in the ibuprofen group compared with the placebo group ( $P < .05$ ).

tension were reported at similar rates in all treatment groups:

#### COMMENT

The discovery of 2 isoforms of COX, the target enzyme inhibited by NSAIDs, has led to a number of questions con-

cerning the role of inhibiting COX-1 vs COX-2 in terms of the efficacy and safety of this widely prescribed class of drugs. Previous work has demonstrated that specific inhibitors of COX-2 are efficacious in the treatment of OA,<sup>37</sup> but left open the question of how that efficacy compares with NSAIDs, which inhibit both COX-1 and COX-2: In this report, we demonstrated that the efficacy of rofecoxib, which specifically inhibits COX-2, was comparable with that of a high dose of the NSAID ibuprofen. Importantly, we characterized the effect of rofecoxib on a variety of the clinical manifestations of OA, and in all cases, we found the efficacy of rofecoxib to be comparable with ibuprofen. These results were obtained in a large, diverse population of patients from 26 different countries, and the results were consistent across race, age, sex, study joint, and prior OA medication use (NSAID vs acetaminophen). Our data also demonstrated that rofecoxib, 12.5 and 25 mg, provided comparable clinical efficacy. Based upon these and other data, it is recommended that 12.5 mg be used as the initial dose of rofecoxib for the treatment of OA.<sup>38</sup>

The NSAIDs are associated with a number of toxic effects, the most important of which are related to the GI tract and the kidney. To firmly establish an improved safety profile of rofecoxib in contrast to NSAIDs, it is important that the safety profiles be compared using doses that provide equivalent efficacy. This study rigorously demonstrated that both once-daily doses (12.5 mg and 25 mg) of rofecoxib

**Table 2. Efficacy Results by End Point According to Treatment Assignment\***

Efficacy End Points	Placebo (n = 74)	Rofecoxib, 12.5 mg (n = 244)	Rofecoxib, 25 mg (n = 242)	Ibuprofen, 2400 mg (n = 249)
<b>Primary</b>				
Pain walking on a flat surface†	-18.92 (-23.72 to -14.12)	-34.32‡ (-37.03 to -31.60)	-35.07‡ (-37.82 to -32.33)	-33.55‡ (-36.26 to -30.84)
Patient global assessment of response to therapy§	-1.56 (-1.77 to -1.36)	-2.28‡ (-2.39 to -2.16)	-2.44‡ (-2.56 to -2.33)	-2.22‡ (-2.34 to -2.11)
Investigator global assessment of disease status§	-1.00 (-1.17 to -0.83)	-1.47‡ (-1.56 to -1.37)	-1.59‡ (-1.68 to -1.49)	-1.40‡ (-1.50 to -1.31)
<b>Secondary</b>				
Physical function subscale†	-8.76 (-12.72 to -4.79)	-18.73‡ (-20.98 to -16.49)	-20.64‡ (-22.91 to -18.37)	-18.06‡ (-20.30 to -15.82)
Pain subscale†	-11.89 (-15.98 to -7.80)	-23.37‡ (-25.68 to -21.05)	-24.78‡ (-27.13 to -22.44)	-22.89‡ (-25.21 to -20.58)
Stiffness subscale†	-8.88 (-13.38 to -4.38)	-21.24‡ (-23.77 to -18.70)	-20.79‡ (-23.33 to -18.24)	-20.17‡ (-22.69 to -17.65)
Patient global assessment of disease status†	-10.02 (-14.60 to -5.45)	-26.93‡ (-29.52 to -24.34)	-26.05‡ (-31.66 to -26.43)	-25.28‡ (-27.87 to -22.69)
Patients discontinued because of lack of efficacy, No. (%)	9 (12.2)	8 (3.3)‡	7 (2.9)‡	9 (3.6)‡
Investigator global assessment of response to therapy§	-1.70 (-1.91 to -1.49)	-2.44‡ (-2.56 to -2.32)	-2.56‡ (-2.68 to -2.44)	-2.40‡ (-2.52 to -2.28)
Tenderness in study joint	-0.56 (-0.70 to -0.42)	-0.84‡ (-0.93 to -0.76)	-0.93‡ (-1.01 to -0.85)	-0.82‡ (-0.90 to -0.74)
Acetaminophen usage for rescue, tablets/d	1.36 (1.14 to 1.58)	0.88 (0.74 to 1.01)	0.82 (0.68 to 0.95)	0.99 (0.85 to 1.13)

\*All values are least squares means (95% confidence intervals) except for the end point "patients discontinued because of lack of efficacy."

†Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a visual analog scale of 0 to 100 mm.

‡P ≤ .009 compared with placebo.

§Likert scale (0-4).

||Scale of 0 to 3.

(which specifically inhibits COX-2) provided comparable clinical efficacy with ibuprofen, 800 mg 3 times daily (a dual COX-1 and COX-2 inhibitor). Therefore, it is appropriate to compare the safety and tolerability of rofecoxib, 12.5 and 25 mg, with those of ibuprofen, 2400 mg.

It is important to note that no adverse events unique to the specific inhibition of COX-2 were apparent in the rofecoxib treatment groups as assessed in this 6-week controlled clinical trial. All active treatments were generally well tolerated. Adverse experiences potentially attributable to renal effects of COX inhibition, such as edema, hypertension, weight gain, and changes in blood pressure, were comparable in all treatment groups, including the placebo group.

An important clinical adverse effect of NSAIDs is their propensity to lead to serious upper GI tract events, such as perforations, gastric and duodenal ulcerations, and upper GI tract bleeding. In other clinical studies,<sup>31,32</sup> as assessed by endoscopy, the incidence of abnormalities of the GI mucosae associated with rofecoxib, 25 and 50 mg, was substantially less than that associated with ibuprofen, 800 mg 3 times daily. Our study was not intended to assess endoscopically diagnosed ulcerations and was not large enough or long enough to compare the incidence of serious upper GI tract events. However, in an overview analysis of all clinical trials<sup>39</sup> performed with rofecoxib, including our study, the incidence of serious upper GI tract events was found to be significantly less with rofecoxib compared with NSAIDs.

In summary, we have demonstrated that specific inhibition of COX-2 provides efficacy in the treatment of OA that is comparable with that of high doses of the NSAID ibuprofen. The safety of rofecoxib, 12.5 and 25 mg once daily, was not significantly different from placebo and ibuprofen, 800 mg 3 times daily.

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**FOR THE TREATMENT OF  
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ACUTE PAIN IN ADULTS**

**AN AGENT THAT INHIBITS  
COX-2 WITHOUT INHIBITING COX-1**

**ONCE-DAILY**

**STRENGTH.  
SAFETY.  
QD SIMPLICITY.**

**FOR BOTH OSTEOARTHRITIS  
AND ACUTE PAIN IN ADULTS**

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 nonsteroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

Common adverse events included upper respiratory infection (8.5%), diarrhea (6.5%), nausea (5.2%), and hypertension (3.5%).

Serious gastrointestinal toxicity can occur with or without warning symptoms with NSAIDs.

Please read Brief Summary of  
Prescribing Information on adjacent page.



# VIQXX (rofecoxib tablets and oral suspension)

## Brief Summary of Prescribing Information

**INDICATIONS AND USAGE:** VIQXX is indicated for relief of the signs and symptoms of osteoarthritis (OA), management of acute pain in adults; treatment of primary dysmenorrhea.

**CONTRAINDICATIONS:** VIQXX is contraindicated in patients with known hypersensitivity to rofecoxib or any other component of VIQXX.

VIQXX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactoid-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 GI 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 NSAIDs. Minor upper GI 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 1 in 5 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 1 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.

It is unclear, at the present time, how the above rates apply to VIQXX. Among 3,357 patients who received VIQXX in controlled clinical trials of 6 weeks to 1 year in duration (most were enrolled in 6-month or longer studies) at a daily dose of 12.5 mg to 50 mg, a total of 14 patients experienced a serious upper GI event, using protocol-derived criteria. Two patients experienced an upper GI bleed within 3 months (at Days 62 and 87, respectively) (0.06%). One additional patient experienced an obstruction within 6 months (Day 130) and the remaining patient developed an upper GI bleed within 12 months (Day 322) (0.12%). Approximately 23% of these 3,357 patients were treated with NSAIDs other than VIQXX. It is unclear if this study population is representative of the general population. Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking VIQXX vs comparator NSAID products have not been performed.

NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or GI 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.

Studies have shown that patients with a prior history of peptic ulcer disease and/or GI bleeding and/or GI bleeding, and/or GI bleeding, have a 2- to 4-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, pharmacologic studies have identified several other comorbidities or comorbid conditions that may increase the risk of GI bleeding, such as: treatment with oral corticosteroids, treatment with anticoagulants, longer duration of NSAID therapy, smoking, alcoholism, older age, and poor general health status.

**Anaphylactoid Reactions:** As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to VIQXX. In postmarketing experience, rare cases of anaphylactoid reactions and angioedema have been reported in patients receiving VIQXX. VIQXX 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 PRECAUTIONS, Preexisting Asthma, and CONTRAINDICATIONS and PRECAUTIONS, Preexisting Asthma). Emergency help should be sought in cases where an anaphylactoid reaction occurs.

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

**Pregnancy:** In late pregnancy, VIQXX should be avoided because it may cause premature closure of the ductus arteriosus.

**PRECAUTIONS: General:** VIQXX 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 pharmacologic activity of VIQXX 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 1 or more liver tests may occur in up to 15% of patients taking NSAIDs, and notable elevations of ALT or AST (3- or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials with NSAIDs. In most cases, 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 VIQXX, the incidence of borderline elevations of liver tests at doses of 12.5 mg and 25 mg daily was comparable to the incidence observed with ibuprofen and lower than that observed with diclofenac. In placebo-controlled trials, approximately 0.5% of patients taking rofecoxib (12.5 mg or 25 mg q.d.) 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 VIQXX. Use of VIQXX is not recommended in patients with moderate or severe hepatic insufficiency. If clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g., eosinophilia, rash, etc.), VIQXX 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 an NSAID may cause a dose-dependent reduction in prostaglandin formation and, secondarily, in renal blood flow, which may precipitate acute renal decompensation. Patients at greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those taking diuretics and angiotensin-converting enzyme (ACE) inhibitors, and the elderly. Discontinuation of NSAID therapy is usually followed by recovery to the pretreatment state. Clinical trials with VIQXX at daily doses of 12.5 mg and 25 mg have shown renal effects (e.g., hypertension, edema) similar to those observed with comparator NSAIDs; these occur with an increased frequency with chronic use of VIQXX at doses above the 12.5-mg to 25-mg range (see ADVERSE REACTIONS). Caution should be used when initiating treatment with VIQXX in patients with considerable dehydration. It is advisable to rehydrate patients first and then start therapy with VIQXX. Caution is also recommended in patients with preexisting kidney disease (see WARNINGS, Advanced Renal Disease).

**Hematologic Effects:** Anemia is sometimes seen in patients receiving VIQXX. In placebo-controlled trials, there were no differences in hemoglobin levels between VIQXX and placebo in clinical reports of anemia. Patients on long-term treatment with VIQXX should have their hemoglobin or hematocrit checked if they exhibit any signs or symptoms of anemia or blood loss. VIQXX does not generally affect platelet counts, prothrombin time, or partial thromboplastin time, and does not inhibit platelet aggregation at indicated dosages.

**Fluid Retention and Edema:** Fluid retention and edema have been observed in some patients taking VIQXX (rofecoxib tablets and oral suspension) (see ADVERSE REACTIONS). VIQXX should be used with caution and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.

**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 NSAIDs has been reported in such aspirin-sensitive patients, VIQXX 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:** VIQXX can cause discomfort and, rarely, more serious side effects, such as GI bleeding, which may result in hospitalization and even fatal outcomes. 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 seek 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 promptly report signs or symptoms of GI ulceration or bleeding, skin rash, unexplained weight gain, or edema 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, VIQXX 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 ACE inhibitors. In patients with mild to moderate hypertension, administration of 25 mg daily of VIQXX with the ACE inhibitor benazepril, 10 to 40 mg for 4 weeks with an average increase in mean arterial blood pressure of about 3 mmHg compared to ACE inhibitor alone. This interaction should be given consideration in patients taking VIQXX concomitantly with ACE inhibitors. **Aspirin:** Concomitant administration of low-dose aspirin with VIQXX may result in an increased rate of upper GI events compared to the rate of use of VIQXX alone. At study state, VIQXX 50 mg once daily had no effect on the antiplatelet activity of low-dose (81 mg once daily) aspirin, as assessed by ex vivo platelet aggregation and serum TXB<sub>2</sub> generation in clotting blood. VIQXX is not a substitute for aspirin for cardiovascular prophylaxis. **Cimetidine:** Concomitant use with high doses of cimetidine (800 mg twice daily) increased the cimetidine bioavailability by 21%, the AUC<sub>0-12h</sub> by 23%, and the t<sub>1/2</sub> 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.

**Paracetamol:** Clinical studies, as well as postmarketing observations, have shown that NSAIDs can reduce the analgesic effect of paracetamol 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 postmarketing experience, there have been reports of increases in plasma lithium levels. Thus, when VIQXX and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity. **Methotrexate:** VIQXX 75 mg administered once daily for 10 days increased plasma concentrations of methotrexate by 23%, as measured by AUC<sub>0-24h</sub> in patients receiving methotrexate 7.5 mg 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 coadministered with 75 mg of rofecoxib (89%) had methotrexate plasma concentrations below the measurable limit (5 nmol/L). The effects of the recommended doses for OA (12.5 mg and 25 mg) of VIQXX on plasma methotrexate levels are unknown. Standard monitoring of methotrexate-related toxicity should be continued if VIQXX and methotrexate are administered concomitantly. **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 prednisone or prednisolone. **Rifampin:** Coadministration of VIQXX 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 VIQXX should be considered for the treatment of OA when VIQXX is coadministered with potent inducers of hepatic metabolism. **Warfarin:** Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing VIQXX therapy in patients receiving warfarin in similar doses, 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 postmarketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIQXX 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) (1- and 2-fold the human exposure at 25 mg and 50 mg daily based on AUC<sub>0-24h</sub>) and in male and female rats given oral doses up to 8 mg/kg (1- and 2-fold the human exposure at 25 mg and 50 mg daily based on AUC<sub>0-24h</sub>). There was an increase in the incidence of preneoplastic lesions in the forestomach of male rats given oral doses up to 100 mg/kg (1- and 7-fold human exposure at 25 mg and 50 mg daily based on AUC<sub>0-24h</sub>) and rofecoxib had no effect on fertility in female rats at doses up to 30 mg/kg (1- and 7-fold human exposure at 25 mg and 50 mg daily based on AUC<sub>0-24h</sub>).

**Pregnancy, Teratogenic Effects, Pregnancy Category C:** Rofecoxib was not teratogenic in rats at dosages up to 50 mg/kg/day (1- and 10-fold human exposure at 25 mg and 50 mg daily based on AUC<sub>0-24h</sub>). There was a slight, statistically significant increase in the overall incidence of vertebral malformations only in the rabbit at doses of 50 mg/kg/day (1- or <1-fold human exposure at 25 mg and 50 mg daily based on AUC<sub>0-24h</sub>). There are no studies in pregnant women. VIQXX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects:** Rofecoxib produced preimplantation and postimplantation losses and reduced embryo/fetal survival in rats and rabbits at oral doses  $\geq 10$  and  $\geq 75$  mg/kg/day, respectively (1- and 3-fold [rats] and 2- and <1-fold [rabbits] human exposure based on AUC<sub>0-24h</sub> at 25 mg and 50 mg daily). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent reproductive toxicity in rats and rabbits at oral doses  $\geq 10$  and  $\geq 75$  mg/kg/day, respectively (1- and 3-fold [rats] and 2- and <1-fold [rabbits] human exposure at 25 mg and 50 mg daily based on AUC<sub>0-24h</sub>). In studies in pregnant rats administered single doses of rofecoxib, there was a treatment-related decrease in the diameter of the ductus arteriosus at oral doses  $\geq 10$  mg/kg/day (1- and <1-fold human exposure at 25 mg or 50 mg daily based on AUC<sub>0-24h</sub>). As with other drugs known to inhibit prostaglandin synthesis, use of VIQXX 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 (1- and 3-fold human exposure as measured by the frequency of uterine contractions at 25 mg and 50 mg) and in labor and delivery in pregnant women are unknown. Merck & Co., Inc., maintains a registry to monitor the pregnancy outcomes of women exposed to VIQXX while pregnant. Healthcare providers are encouraged to report any prenatal exposure to VIQXX by calling the Pregnancy Registry at 1-800-938-8989.

**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 VIQXX (rofecoxib tablets and oral suspension) during lactation. The dose tested represents an approximate 18- and 6-fold human exposure at 25 mg and 50 mg daily based on AUC<sub>0-24h</sub>. It is not known whether this drug is excreted in human milk. Because many drugs are known in human milk and because of the potential for serious adverse reactions in nursing infants from VIQXX, 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 VIQXX in OA clinical trials, 1,455 were 65 years of age or older (this included 460 who were 75 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. Dosage adjustment in the elderly is not necessary; however, therapy with VIQXX should be initiated at the lowest recommended dose. In 1 of the studies (6-week, double-blind, randomized clinical trial), VIQXX 12.5 mg or 25 mg once daily was administered to 174 OA patients  $\geq 65$  years of age. The safety profile in this elderly population was similar to that of younger patients treated with VIQXX.

**ADVERSE REACTIONS: OA:** Approximately 3,000 patients with OA were treated with VIQXX; approximately 1,400 patients received VIQXX for 6 months or longer, and approximately 600 patients for 1 year or longer. The following paragraph lists all adverse events, regardless of causality, occurring in at least 2% of patients receiving VIQXX in 6 controlled studies of 6 weeks to 6 months' duration conducted in patients with OA at the therapeutically recommended doses (12.5 mg and 25 mg), which included a placebo and/or positive control group.

Clinical adverse experiences occurring in  $\geq 2.0\%$  of patients treated with VIQXX vs placebo, ibuprofen 2400 mg, or diclofenac 150 mg: **Body as a Whole:** Unspecified abdominal pain, 3.4% (vs 4.1%, placebo; 4.6%, ibuprofen; 5.8%, diclofenac); asthenia/fatigue, 2.2% (vs 1.0%; 2.0%; 2.6%); dizziness, 3.0% (vs 2.2%, 2.7%, 3.4%); influenza-like disease, 2.9% (vs 3.1%, 1.5%; 3.2%); lower extremity edema, 3.7% (vs 1.1%; 3.8%; 3.4%); upper respiratory infection, 8.5% (vs 6.8%, 5.8%, 4.2%); **Cardiovascular System:** Hypertension, 3.3% (vs 1.3%, 3.0%, 1.6%); **Digestive System:** Diarrhea, 6.5% (vs 6.8%, 7.1%, 10.6%); dyspepsia, 3.5% (vs 2.7%, 4.7%, 4.0%); epigastric discomfort, 3.8% (vs 2.8%; 9.2%; 5.4%); heartburn, 4.2% (vs 3.6%; 5.2%; 4.5%); nausea, 5.2% (vs 2.8%; 7.1%; 7.4%); **Eyes:** Eye pain, 4.0% (vs 3.6%; 2.7%); **Ears, Nose, and Throat:** Sinusitis, 2.7% (vs 2.0%; 1.5%; 2.4%); **Musculoskeletal System:** Back pain, 2.2% (vs 1.3%; 1.4%; 2.8%); **Nervous System:** Headache, 4.7% (vs 7.5%; 6.1%; 8.0%); **Respiratory System:** Bronchitis, 2.7% (vs 2.5%; 1.4%; 3.2%); **Urogenital System:** Urinary tract infection, 2.8% (vs 2.0%; 2.5%; 3.6%).

The general safety profile of VIQXX 30 mg q.d. in OA clinical trials of up to 6 months (476 patients) was similar to that of VIQXX at the recommended OA doses of 12.5 mg and 25 mg q.d., except for a higher incidence of GI symptoms (abdominal pain, epigastric pain, heartburn, nausea, and vomiting), lower extremity edema (6.3%), and hypertension (8.2%).

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

**Body as a Whole:** abdominal distention, abdominal tenderness, abscess, chest pain, chills, contusion, cyst, diaphragmatic hernia, fever, fluid retention, flushing, lung 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, dysuria, esophagitis, flatulence, gastric disorder, gastritis, gastroenteritis, hemorrhoids, hemorrhoids, infectious gastroenteritis, oral infection, oral lesion, oral ulcer, vomiting. **Eyes:** Eye pain, Eye, nose, and throat allergic rhinitis, blurred vision, conjunctivitis, conjunctivitis, dry throat, epiphora, keratitis, nasal congestion, nasal secretion, ophthalmic injection, otitis, otitis, otitis media, pharyngitis, tonsillitis, tonsillitis. **Immune System:** allergy, hypersensitivity, insect bite reaction. **Metabolism and Nutrition:** appetite change, hypercholesterolemia, weight gain. **Musculoskeletal System:** arm pain, arthralgia, arthralgia, back strain, muscle cramp, cartilage trauma, joint swelling, muscular cramp, muscular disorder, muscular weakness, musculoskeletal stiffness, myalgia, osteoarthritis, tendonitis, traumatic arthropathy, wrist fracture. **Nervous System:** hypesthesia, insomnia, median nerve neuropathy, migraine, muscular spasm, parosmia, social phobia, somnolence, vertigo. **Psychiatric:** anxiety, depression, mental status 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, periorificial dermatitis, rash, skin erythema, urticaria, vesicles. **Urogenital System:** breast mass, cystitis, dysuria, menopause symptoms, menstrual disorder, nocturia, urinary retention, vaginitis.

The following serious adverse events have been reported rarely (estimated  $<0.1\%$  in patients taking VIQXX, regardless of causality. Cases reported only in the postmarketing experience are indicated in italics).

**Cardiovascular:** cerebrovascular accident, congestive heart failure, deep venous thrombosis, myocardial infarction, pulmonary embolism, transient ischemic attack, unstable angina. **GI:** cholecystitis, colitis, colonic malignant neoplasm, duodenal perforation, duodenal ulcer, esophageal ulcer, gastric perforation, gastric ulcer, GI bleeding, hepatitis, intestinal obstruction, jaundice, pancreatitis. **Hemic and Lymphatic:** agranulocytosis, leukopenia, lymphoma, thrombocytopenia. **Infections:** anaphylactoid reaction, angioedema. **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, prostate malignant neoplasm, urinary incontinence, worsening chronic renal failure.

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

**Analgesia, Including Primary Dysmenorrhea:** Approximately 1,000 patients were treated with VIQXX in analgesia studies. All patients in postmenstrual survey pain studies received only a single dose of study medication. Patients in primary dysmenorrhea studies may have taken up to 3 daily doses of VIQXX, and those in the postorthopedic surgery pain study were prescribed 5 daily doses of VIQXX.

The adverse-experience profile in the analgesia studies was generally similar to those reported in the OA studies. The following additional adverse experience, which occurred at an incidence of 22% of patients treated with VIQXX, was observed in the postmenstrual survey study: postmenstrual extrusion avulsion (dry socket).

In 110 patients treated with VIQXX (average age: 65 years) in the postorthopedic surgery pain study, the most commonly reported adverse experiences were constipation, fever, and nausea.

**DOSE AND ADMINISTRATION:** VIQXX is administered orally. The lowest dose of VIQXX should be sought for each patient.

OA: The recommended starting dose of VIQXX 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 VIQXX is 50 mg once daily. Subsequent doses should be 50 mg once daily for 2 to 3 days. Use of VIQXX for more than 3 days in management of pain has not been studied.

VIQXX Tablets may be taken with or without food.

**Oral Suspension:** VIQXX Oral Suspension 12.5 mg/mL or 25 mg/mL may be substituted for VIQXX Tablets 12.5 mg or 25 mg, respectively, in any of the above indications. Shake before use.

For more detailed information, consult your Merck representative and read the full Prescribing Information.

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Dear Doctor:

Thank you for your interest in this reprint, "Rofecoxib, a Specific Inhibitor of Cyclooxygenase 2, with Specific Efficacy Comparable with that of Diclofenac Sodium: Results of a One-Year, Randomized, Clinical Trial in Patients with Osteoarthritis of the Knee and Hip," by Grant W. Cannon et al, published in *Arthritis & Rheumatism*, Volume 43, Number 5, May 2000. We are pleased to provide this article to you as requested.

This study, a randomized, double-blind, active-comparator-controlled trial in 784 adults, compared the clinical efficacy of VIOXX<sup>®</sup> (rofecoxib) with that of diclofenac. The study also evaluated the safety and tolerability of VIOXX.

Patients were randomized to one of three treatment groups: 12.5-mg VIOXX once daily, 25-mg VIOXX once daily, or 50-mg diclofenac three times a day. Clinical efficacy and safety were evaluated over a one-year continuous treatment period. Patients could receive additional arthritis medication during the last six months.

VIOXX is indicated for relief of the signs and symptoms of osteoarthritis, the management of acute pain in adults (see CLINICAL STUDIES), and the treatment of primary dysmenorrhea.

**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 other allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

VIOXX is **not** a sulfonamide; therefore, VIOXX has **no** sulfonamide contraindication.

Serious gastrointestinal toxicity can occur with or without warning symptoms with NSAIDs.

Before prescribing VIOXX, please read the accompanying complete Prescribing Information. Thank you for your interest in this information about VIOXX.

Very truly yours,

Gail A. Ryan  
Professional Services

Enclosure: Prescribing Information for VIOXX

VIOXX is a registered trademark of Merck & Co., Inc.

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## ROFECOXIB, A SPECIFIC INHIBITOR OF CYCLOOXYGENASE 2, WITH CLINICAL EFFICACY COMPARABLE WITH THAT OF DICLOFENAC SODIUM

Results of a One-Year, Randomized, Clinical Trial in Patients with  
Osteoarthritis of the Knee and Hip

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ROFECOXIB PHASE III PROTOCOL 035 STUDY GROUP

**Objective.** To compare the clinical efficacy of rofecoxib, a specific inhibitor of cyclooxygenase 2 (COX-2), with that of diclofenac in patients with osteoarthritis (OA) and to evaluate the safety and tolerability of rofecoxib.

**Methods.** We performed a randomized, double-blind, active comparator-controlled trial in 784 adults with OA of the knee or hip. Patients were randomized to 1 of 3 treatment groups: 12.5 mg of rofecoxib once daily, 25 mg of rofecoxib once daily, and 50 mg of diclofenac 3 times daily. Clinical efficacy and safety were evaluated over a 1-year continuous treatment period.

**Results.** Rofecoxib at dosages of 12.5 and 25 mg demonstrated efficacy that was clinically comparable to that of diclofenac, as assessed by all 3 primary end points according to predefined comparability criteria. Results from secondary end points were consistent with those of the primary end points. There were small statistical differences favoring diclofenac for 2 of the end points. All treatments were well tolerated.

**Conclusion.** Rofecoxib was well tolerated and provided efficacy that was clinically comparable, ac-

ording to predefined statistical criteria, to that of 150 mg of diclofenac per day in this 1-year study. Specific inhibition of COX-2 provided therapeutic efficacy in OA.

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used in the treatment of osteoarthritis (OA) (1,2). Although NSAIDs effectively control mild-to-moderate joint pain associated with OA, their use is accompanied by the risk of significant gastrointestinal (GI) toxicity, including GI perforation, ulceration, and bleeding (PUB) (3-5).

NSAIDs act by inhibiting the synthesis of prostaglandins by the enzyme cyclooxygenase (COX) (6,7). Two COX isoforms are now recognized. COX-1, which is constitutively expressed, sustains the routine physiologic function of prostaglandins, including gastric mucosal protection; COX-2 is induced chiefly in response to pathologic processes, including pain and inflammation (5-8). Prostaglandins synthesized by the inducible COX-2 isoform mediate acute inflammatory responses in animal models (9).

In vitro and ex vivo assays have shown that NSAIDs are non-isoform specific, inhibiting both the COX-1 and COX-2 isoforms (10-16). Since prostaglandins are involved in the maintenance of GI mucosal integrity and since only the COX-1 isoform is present in the normal GI mucosa, the GI toxicity of NSAIDs has been proposed to result largely from inhibition of COX-1 activity (12,17-20). The therapeutic effects of NSAIDs may be primarily attributable to COX-2 inhibition (9,21,22). Therefore, agents that specifically inhibit COX-2 were developed and evaluated because of their potential to provide clinical efficacy comparable to

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that of NSAIDs with a reduced risk of GI toxicity (23-25).

Rofecoxib (VIOXX®; Merck, Rahway, NJ) is a specific inhibitor of COX-2 in humans. Using *ex vivo* human whole blood assays, rofecoxib showed dose-related inhibition of COX-2 activity (26). The degree of COX-2 inhibition was similar to that of NSAIDs. At doses of 15-40 times the proposed clinical dose, rofecoxib had no dose-dependent inhibition of COX-1 (27).

This report describes the results of a large, randomized, clinical trial comparing rofecoxib, 12.5 and 25 mg once daily, with diclofenac sodium, 50 mg 3 times daily, in the treatment of patients with knee and hip OA. In this study, rofecoxib provided efficacy in OA that, according to predefined statistical criteria, was clinically comparable to a high dose of the NSAID diclofenac. In a study using serial endoscopy for the presence of ulcers in OA patients, rofecoxib demonstrated a GI safety profile equivalent to that of placebo and significantly better than that of ibuprofen (28). Our findings, together with those reported by Laine et al (28), show that in the treatment of OA, rofecoxib is as effective as diclofenac and has the potential to improve the GI safety profile.

## PATIENTS AND METHODS

All patients gave written informed consent before screening and enrollment in the study. The study protocol and procedures were approved by the institutional review boards for all investigative sites. The investigators who participated in the Rofecoxib Protocol 035 Study Group are listed in Appendix A.

**Study design.** Patients were screened (screening visit) to ensure study eligibility. Upon confirmation of eligibility (see entry criteria), patients were randomized (randomization visit) by a computer-generated allocation schedule to 1 of 3 treatment groups: rofecoxib 12.5 mg once daily, rofecoxib 25 mg once daily, or diclofenac 50 mg 3 times daily (150 mg/day). Study blinding was maintained by using a matching placebo for each study medication. Patients took 3 tablets each morning and 1 tablet at both midday and evening. Patients were provided open-label acetaminophen (maximum dosage of 2.6 gm/day) that could be taken for OA pain that was not adequately controlled by the study medication.

Patients returned to the study center following 2, 4, 8, 12, 19, 26, 33, 39, 45, and 52 weeks of therapy to assess both efficacy and safety. Patients who did not enter a voluntary extension at the end of the 1-year treatment period returned 7-10 days after their last dose of study medication for post-therapy safety assessments.

**Entry criteria.** Patients were a minimum of 40 years old and had both clinical and radiographic evidence of OA. Patients with OA of the knee or hip were eligible for study. Radiographic criteria for OA of the knee were joint space narrowing and the presence of osteophytes; the radiographic criterion for OA of the hip was joint space narrowing. The study joint (either the knee or the hip) had to be the primary

source of pain or disability. Patients were in functional class I, II, or III according to the Steinbrocker criteria (29). The study included 2 groups of OA patients, based on the treatment they received for OA at the time of enrollment: those who took NSAIDs and those who took acetaminophen.

The NSAID group was assessed at the screening visit, and patients who satisfied entry criteria discontinued their NSAID therapy. Following a washout period, patients' pain when walking was assessed on a patient-reported 100-mm visual analog scale (VAS). Patients were randomized into the study if they had at least moderate pain when walking (40 mm) and a minimum increase in pain when walking (15 mm) compared with the level at screening. In addition, the physician's assessment of disease status had to be worse compared with the screening level.

The acetaminophen group was randomized if at both the screening and randomization visits (no acetaminophen allowed within 12 hours of assessments), the patients reported at least moderate pain when walking (40 mm). In addition, the patient's and physician's assessments of disease status had to be fair, poor, or very poor.

Women were postmenopausal or demonstrably non-gravid. Patients were excluded if they had significant renal impairment, clinically significant abnormalities on physical or laboratory examinations at the screening visit, positive results on fecal occult blood testing, class III/IV angina or uncontrolled congestive heart failure, uncontrolled hypertension, a stroke or transient ischemic attack within 2 years of study, active hepatic disease, a history of recent neoplastic disease, or an allergy to acetaminophen or NSAIDs. Patients were excluded if they required aspirin at any dose, corticosteroids, warfarin, or ticlopidine.

Patients with a history of gastroduodenal ulcer or GI bleeding were allowed to participate.

**Efficacy measurements and end points.** Well-validated measurements of efficacy were obtained at screening, randomization, and following 2, 4, 8, 12, 26, 39, and 52 weeks of treatment. At each of these visits, the patients completed the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (30), and both the patients and the physicians completed an assessment of disease status. Patients and physicians completed an assessment of response to therapy following 2, 4, 8, 12, and 26 weeks of treatment.

There were 3 primary end points for this study: pain when walking (100-mm VAS, which is question 1 of the WOMAC), patient's assessment of response to therapy (5-point scale, where 0 = none and 4 = excellent), and physician's assessment of disease status (5-point scale, where 0 = very poor and 4 = very well). All 3 end points were used to determine clinical and statistical comparability, as described in the statistical section (see below).

Other end points were patient's assessment of disease status (100-mm VAS, where 0 = very well and 100 = very poor), physician's assessment of response to therapy (5-point scale, where 0 = none and 4 = excellent), WOMAC subscales of Pain, Stiffness, and Functional Ability (100-mm VAS), study-joint tenderness (0-3 scale, where 0 = no pain and 3 = patient states that there is pain; winces and withdraws), and amount of rescue acetaminophen consumed (number of 325-mg tablets).

**Safety assessments.** Spontaneously reported adverse experiences were recorded throughout the study. Vital signs

**Table 1.** Baseline characteristics of the patients, according to treatment group\*

Characteristic	Rofecoxib		Diclofenac,	Total (n = 784)
	12.5 mg (n = 259)	25 mg (n = 257)	150 mg (n = 268)	
Female sex, no. (%)	169 (65.3)	175 (68.1)	185 (69.0)	529 (67.5)
Race, no. (%)				
White	236 (91.1)	229 (89.1)	237 (88.4)	702 (89.5)
African American	19 (7.3)	23 (8.9)	23 (8.6)	65 (8.3)
Other	4 (1.5)	5 (1.9)	8 (3.0)	17 (2.2)
Age, mean $\pm$ SD years	62.8 $\pm$ 10.2	62.8 $\pm$ 10.3	62.5 $\pm$ 10.1	63.6 $\pm$ 10.2
Weight, mean $\pm$ SD kg	92.4 $\pm$ 22.2	87.9 $\pm$ 19.6	88.0 $\pm$ 21.0	89.4 $\pm$ 21.0
Duration of OA, mean $\pm$ SD years	11.1 $\pm$ 8.9	11.5 $\pm$ 8.7	11.4 $\pm$ 9.4	8.7 $\pm$ 9.0
Functional class, no. (%)				
Class I	31 (12.0)	39 (15.2)	38 (14.2)	109 (13.9)
Class II	173 (66.8)	176 (68.5)	168 (62.7)	517 (65.9)
Class III	54 (20.8)	42 (16.3)	62 (23.1)	158 (20.2)
Study joint, no. (%)				
Hip	61 (23.6)	68 (26.5)	61 (22.8)	190 (24.2)
Knee	198 (76.4)	189 (73.5)	207 (77.2)	594 (75.8)
Previous OA medication use, no. (%)				
NSAIDs	240 (92.7)	238 (92.6)	242 (90.3)	720 (91.8)
Acetaminophen	19 (7.3)	19 (7.4)	26 (9.7)	64 (8.2)
Primary outcome measure†				
Pain when walking (WOMAC), 0–100-mm VAS	75.9 $\pm$ 15.0	77.5 $\pm$ 14.7	75.8 $\pm$ 15.4	76.4 $\pm$ 15.0
Physician's assessment of disease status, 0–4 Likert scale	2.9 $\pm$ 0.7	2.9 $\pm$ 0.7	3.0 $\pm$ 0.7	2.9 $\pm$ 0.7

\* Duration of osteoarthritis (OA) was determined by patient report. Functional class was determined according to the Steinbrocker criteria. NSAIDs = nonsteroidal antiinflammatory drugs; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; VAS = visual analog scale.

† The third primary outcome measure, patient's assessment of response to therapy, was not examined past week 26 and does not have baseline (randomization) values because it assessed the patient's response to therapy.

were monitored at every visit. Laboratory investigations, including hematology, blood chemistry, and a urinalysis, were performed at all visits. For all clinical adverse experiences, the investigator recorded the intensity, the relation to test drug, the outcome, and any action taken. The investigator also determined if a laboratory adverse event was study-drug related.

**Statistical analysis.** This study tested the hypothesis that rofecoxib, 12.5 mg and 25 mg once daily, would have clinical efficacy comparable to that of diclofenac, 50 mg 3 times

daily. As a comparability trial, specific predefined criteria were established. Clinical comparability was declared if the following criteria were met: for all 3 primary end points, the 95% confidence intervals (95% CIs) of the difference in the mean treatment response between 2 treatments were within  $\pm 10$  mm on a 100-mm VAS and  $\pm 0.5$  on a Likert scale. These clinical comparability bounds are more conservative than those proposed by a consensus of academic rheumatologists and employed in a study comparing meloxicam with diclofenac (31,32). This study had >99% power to demonstrate compa-

**Table 2.** Numbers of patients who entered, completed, and discontinued the study, according to treatment group

Study status	Rofecoxib		Diclofenac,	Total
	12.5 mg	25 mg	150 mg	
Entered the study, no. of patients	259	257	268	784
Completed the study, no. (%)	161 (62.2)	142 (55.3)	145 (54.1)	448 (57.1)
Discontinued the study, no. (%)	98 (37.8)	115 (44.7)	123 (45.9)	336 (42.9)
Clinical adverse experience	37 (14.3)	32 (12.5)	41 (15.3)	110 (14.0)
Laboratory adverse experience	1 (0.4)	2 (0.8)	14 (5.2)	17 (2.2)
Lack of efficacy	36 (13.9)	56 (21.8)	43 (16.0)	135 (17.2)
Deviation from protocol	10 (3.9)	12 (4.7)	11 (4.1)	33 (4.2)
Patient withdrew consent	9 (3.5)	9 (3.5)	11 (4.1)	29 (3.7)
Other*	5 (1.9)	4 (1.6)	3 (1.1)	12 (1.5)

\* Includes patients who moved and patients who were lost to followup.

rable efficacy (according to the criteria cited) between 25 mg of rofecoxib and diclofenac if their true difference is 0.

For the determination of comparability, the 3 primary end points were analyzed as the averaged response over the 52-week treatment period (first 26 weeks only for patient's assessment of response to therapy). All data collected from discontinuation and unscheduled visits were included in this analysis; no missing values were imputed. The comparability analysis was also performed on data from the first 12 weeks and the first 26 weeks.

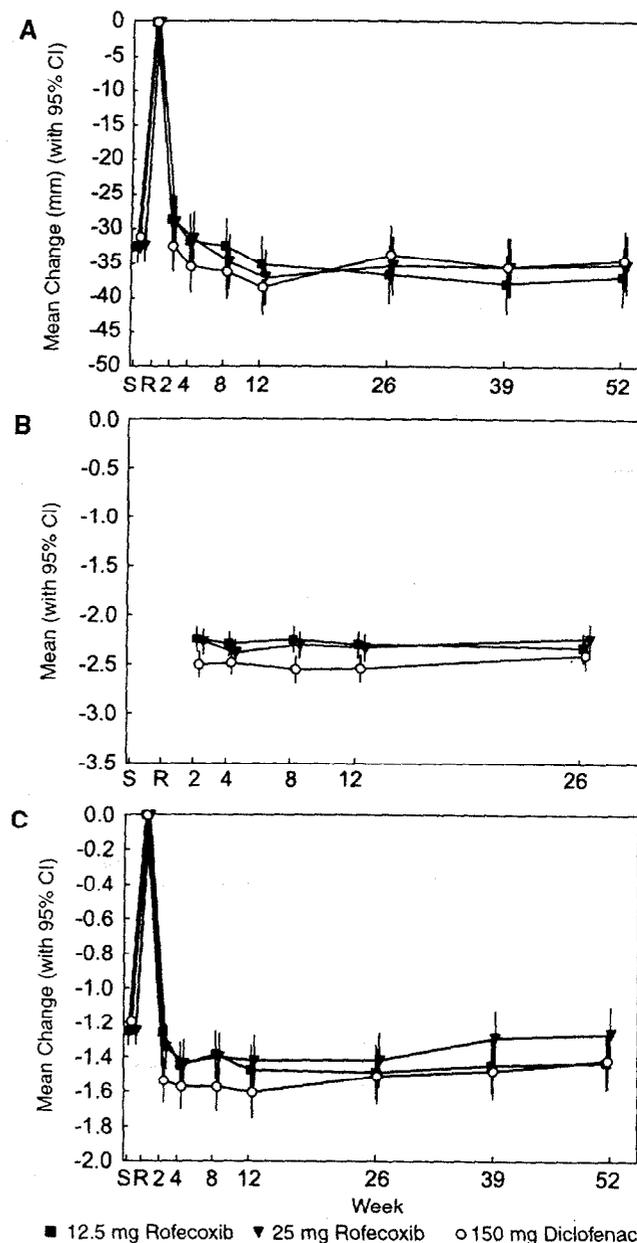
The responses of primary and secondary end points were analyzed using an analysis of covariance model, with treatment, study center, and history of ulcer or upper GI bleeding as main effects, and baseline as the covariate. For end points without baseline measurements (i.e., patient's/physician's assessment of response to therapy), the baseline value of a relevant variable (i.e., patient's/physician's assessment of disease status) was used as the covariate in the model.

## RESULTS

Between November 1996 and April 1997, 1,128 patients were screened, and 784 (69.5%) were enrolled into the study. Patients not randomized were excluded for a variety of reasons, including failure to meet OA diagnostic criteria (13.8%), abnormalities found on screening physical or laboratory examinations (12.1%), failure to satisfy randomization OA activity criteria (1.3%), and their reconsideration of participation in the study (4.2%). All treatment groups had similar baseline characteristics and primary efficacy outcome measures at enrollment (Table 1). All randomized patients with OA of the knee and 96% of those with OA of the hip fulfilled the American College of Rheumatology classification criteria for OA of those regions (33,34).

A total of 448 of the 784 patients (57.1%) completed 1 year of study therapy (Table 2); the overall discontinuation incidence was similar among treatment groups. There were no statistically significant differences in the incidence of discontinuation because of lack of efficacy of the study therapy or clinical adverse experience among the treatment groups. The increased discontinuation rate because of laboratory adverse experiences in the diclofenac group was due to elevations in serum transaminases, as discussed later in the Results (see below).

**Efficacy.** Figure 1 presents the response over time for all 3 primary end points. Both pain when walking and physician's assessment of disease status, the 2 end points evaluated at baseline (randomization), demonstrated significant improvements from baseline for all treatment groups. The mean response for the primary end point of patient's assessment of response to therapy was similar among all treatment groups. This end point was not examined past week 26 and does not



**Figure 1.** Treatment response over time for the 3 primary clinical efficacy end points: **A**, pain when walking (baseline mean 76.4 mm on a 100-mm visual analog scale), **B**, patient's assessment of response to therapy (not assessed at baseline visit), and **C**, physician's assessment of disease status (baseline mean 2.9 on a 5-point scale, where 0 = very poor and 4 = very well). Scales in **A** and **C** were normalized to the randomization mean; the scale in **B** was inverted for consistency with other end points. On all graphs, decreasing values indicate improvement. S = screening visit; R = randomization visit; 95% CI = 95% confidence interval.

have baseline values because it assessed the patients' response to therapy.

For all primary end points, treatment responses

**Table 3.** Comparability analysis for the 3 primary end points over 1 year or 6 months of treatment, as indicated\*

Primary end point	Comparing 25 mg of rofecoxib with 150 mg of diclofenac	Comparing 12.5 mg of rofecoxib with 150 mg of diclofenac
Pain when walking (WOMAC question 1), 0–100-mm VAS	1.98 (–1.66, 5.62)	1.81 (–1.85, 5.44)
Patient's assessment of response to therapy, 0–4 Likert scale†	0.19 (0.05, 0.33)	0.24 (0.10, 0.38)
Physician's assessment of disease status, 0–4 Likert scale	0.17 (0.05, 0.29)	0.13 (0.01, 0.25)

\* Comparability was defined as the difference in the least squares mean (95% confidence interval), and must be within  $\pm 10$  mm on the visual analog scale (VAS) and  $\pm 0.5$  units on the Likert scale. Positive mean differences favor diclofenac over rofecoxib. WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index.

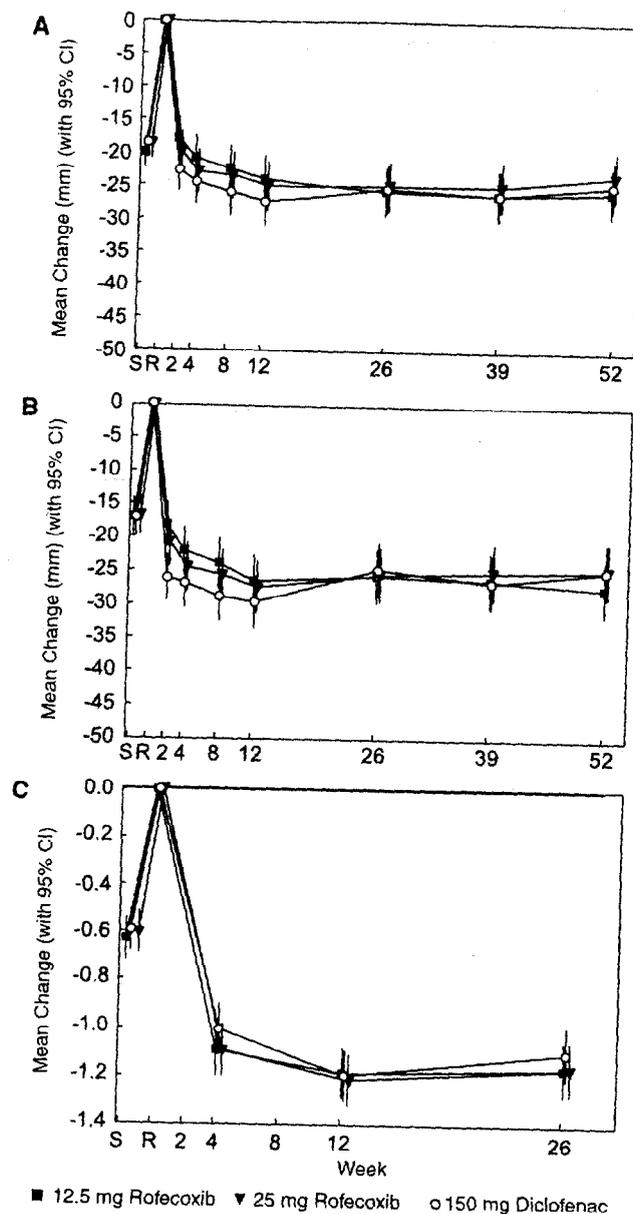
† Data for this end point were not collected after week 26; therefore, the analysis concerns the first 26 weeks of treatment.

were seen within 2 weeks (first time point measured) for all treatment groups. The treatment responses were sustained throughout the entire year of treatment (or 26 weeks for patient's assessment of response to therapy) at a generally consistent level.

The primary hypothesis of this study was that rofecoxib would provide comparable clinical efficacy to that of diclofenac in the treatment of OA. To test this hypothesis, comparability criteria for the 3 primary end points were prespecified (as discussed in Patients and Methods). The difference in the mean treatment response between 2 treatments is calculated as treatment A minus treatment B, and this difference has an associated 95% CI. The 2 treatments would be considered clinically comparable if the 95% CI of the difference does not extend beyond the predefined bound of  $\pm 10$  mm on the VAS and  $\pm 0.5$  on the Likert scale.

Table 3 presents the comparability data. For all 3 primary end points, the 95% CIs for the difference in the mean treatment response for each of the treatment pairs (25 mg of rofecoxib and diclofenac; 12.5 mg of rofecoxib and diclofenac) were within the predefined comparability bound. Thus, both 12.5 and 25 mg of rofecoxib demonstrated clinical efficacy comparable to that of 150 mg diclofenac over 1 year of continued treatment. The same conclusion was reached when comparability was analyzed for the first 12 weeks or the first 26 weeks of treatment.

There were small differences favoring diclofenac compared with rofecoxib for 2 end points that reached



**Figure 2.** Treatment responses over time for the 3 secondary end points: **A**, Physical Function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (baseline mean 69.6 on a 100-mm visual analog scale [VAS]), **B**, Stiffness subscale of the WOMAC (baseline mean 72.9 on a 100-mm VAS), and **C**, study-joint tenderness (baseline mean 2.0 on a 0–3 scale, where 0 = no pain and 3 = patient states that there is pain; winces and withdraws). Study-joint tenderness was not assessed after week 26. Scales were normalized to the randomization mean. On all graphs, decreasing values indicate improvement. S = screening visit; R = randomization visit; 95% CI = 95% confidence interval.

statistical significance: patient's assessment of response to therapy and physician's assessment of disease status.

**Table 4.** Summary of secondary efficacy end points over the 12-month treatment period\*

Efficacy end point	Rofecoxib		Diclofenac, 150 mg (n = 268)
	12.4 mg (n = 259)	25 mg (n = 257)	
Pain subscale (WOMAC), 0-100-mm VAS	-26.7 (-29.5, -23.9)	-27.3 (-30.1, -24.42)	-29.6 (-32.4, -26.8)
Physical Function subscale (WOMAC), 0-100-mm VAS	-23.4 (-26.4, -20.4)	-23.8 (-26.8, -20.7)	-25.8 (-28.9, -22.8)
Stiffness subscale (WOMAC), 0-100-mm VAS	-24.5 (-27.7, -21.3)	-25.2 (-28.4, -22.0)	-27.7 (-30.9, -24.5)
Patient's assessment of disease status, 0-100-mm VAS	-28.5 (-31.7, -25.3)	-27.1 (-30.3, -23.9)	-31.5 (-34.7, -28.3)
Physician's assessment of response to therapy, 0-4 Likert scale†	-2.5 (-2.66, -2.43)	-2.5 (-2.61, -2.39)	-2.8 (-2.9, -2.6)
Study-joint tenderness, 0-3 Likert scale	-1.1 (-1.2, -1.0)	-1.2 (-1.3, -1.1)	-1.1 (-1.2, -1.0)
Acetaminophen use (for rescue), tablets/day	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.7 (0.6, 0.8)

\* Values are the least squares mean (95% confidence interval), representing the mean change from the time of randomization. Negative values indicate improvement in the end point compared with randomization (visit 2), except for acetaminophen use. See Table 1 for definitions.

† Data for this end point were not collected after week 26; therefore, the analysis concerns the first 26 weeks of treatment.

However, these differences and their respective 95% CIs were within the comparability bounds predefined for this study.

OA is a complex disease with multiple clinical manifestations. Secondary end points were collected to assess the response to treatment in a variety of domains. The secondary end points of the WOMAC Stiffness subscale, WOMAC Physical Function subscale, and study-joint tenderness (Figure 2) demonstrated significant changes from baseline in all treatment groups. Results for additional secondary end points were consistent with the finding of clinical comparability among treatment groups (Table 4).

The consistency of the treatment effects of rofecoxib and diclofenac among patients of various subgroups was compared. Treatment-by-factor analysis for the 3 primary end points showed that there was no statistically significant interaction with treatment for various subgroups, including location of the study joint (knee or hip), previous OA medication (NSAID or acetaminophen), age, and sex.

**Safety.** All safety data are reported for the entire 1-year treatment period. The incidence of each clinical adverse event and drug-related (as assessed by the investigator) adverse event was similar among the treatment groups. The most frequent adverse events were upper respiratory infection and sinusitis; the most frequent GI adverse events were nausea, diarrhea, and heartburn (Table 5). The differences in incidence of GI adverse events were not statistically significant.

The incidence of patients who discontinued the study because of clinical adverse events was similar among the 3 treatment groups (Table 2). The majority of discontinuations were because of adverse experiences related to the GI or cardiovascular systems. Patients discontinued because of GI symptoms at a similar incidence (4.6%, 3.1%, and 3.7% in the 12.5-mg rofecoxib, 25-mg rofecoxib, and diclofenac groups, respec-

tively). Patients discontinued because of cardiovascular events at a similar incidence (2.3%, 3.1%, and 3.7% in the 12.5-mg rofecoxib, 25-mg rofecoxib, and diclofenac groups, respectively). The most frequent individual adverse experiences resulting in discontinuation were diarrhea, dyspepsia, epigastric discomfort, and myocardial infarction (Table 5). No single adverse experience accounted for discontinuation in >2 patients per treatment group.

A total of 2, 2, and 3 patients in the 12.5-mg rofecoxib, 25-mg rofecoxib, and diclofenac groups, respectively, experienced a symptomatic gastric or duodenal ulcer. There were no episodes of GI bleeding in this study.

The incidence of drug-related lower extremity

**Table 5.** Summary of adverse experiences\*

	Rofecoxib		Diclofenac, 150 mg (n = 268)
	12.5 mg (n = 259)	25 mg (n = 257)	
Any clinical adverse event	86.9	84.0	86.2
Any drug-related clinical adverse event†	30.9	30.4	32.5
Most frequent adverse event			
Upper respiratory infection	23.9	25.7	17.9
Sinusitis	8.9	7.4	7.1
Most frequent GI adverse event			
Nausea	6.2	7.4	9.7
Diarrhea	6.9	12.1	10.4
Heartburn	5.4	5.1	3.0
Any laboratory adverse event	14.4	18.4	27.4
Discontinuation due to adverse event			
Diarrhea	0.4	0.8	0.4
Dyspepsia	0.4	0.8	0.0
Epigastric discomfort	0.8	0.0	0.7
Myocardial infarction	0.4	0.4	0.7

\* Values are percentages of patients. GI = gastrointestinal.

† Determined by the investigator to be possibly, probably, or definitely medication related.

**Table 6.** Blood pressure and serum creatinine levels over time\*

Variable, treatment group	Screening visit	Week 12	Week 26	Week 52
Systolic blood pressure (mm Hg)				
Rofecoxib 12.5 mg	136.7 ± 16.5	136.2 ± 15.6	134.4 ± 17.3	136.8 ± 17.4
Rofecoxib 25 mg	135.6 ± 15.4	136.9 ± 16.7	133.9 ± 14.9	136.8 ± 17.0
Diclofenac 150 mg	136.4 ± 16.3	134.9 ± 14.7	134.3 ± 15.4	133.7 ± 16.3
Diastolic blood pressure (mm Hg)				
Rofecoxib 12.5 mg	80.8 ± 7.8	79.9 ± 8.2	80.1 ± 8.2	80.2 ± 8.0
Rofecoxib 25 mg	80.4 ± 8.4	81.0 ± 9.4	79.5 ± 9.0	81.5 ± 9.6
Diclofenac 150 mg	81.0 ± 8.7	79.9 ± 9.3	79.1 ± 9.7	79.8 ± 8.9
Serum creatinine (mg/dl)				
Rofecoxib 12.5 mg	1.14 ± 0.2	1.15 ± 0.2	1.14 ± 0.2	1.11 ± 0.2
Rofecoxib 25 mg	1.13 ± 0.2	1.16 ± 0.2	1.16 ± 0.2	1.13 ± 0.2
Diclofenac 150 mg	1.13 ± 0.2	1.15 ± 0.2	1.15 ± 0.2	1.10 ± 0.2

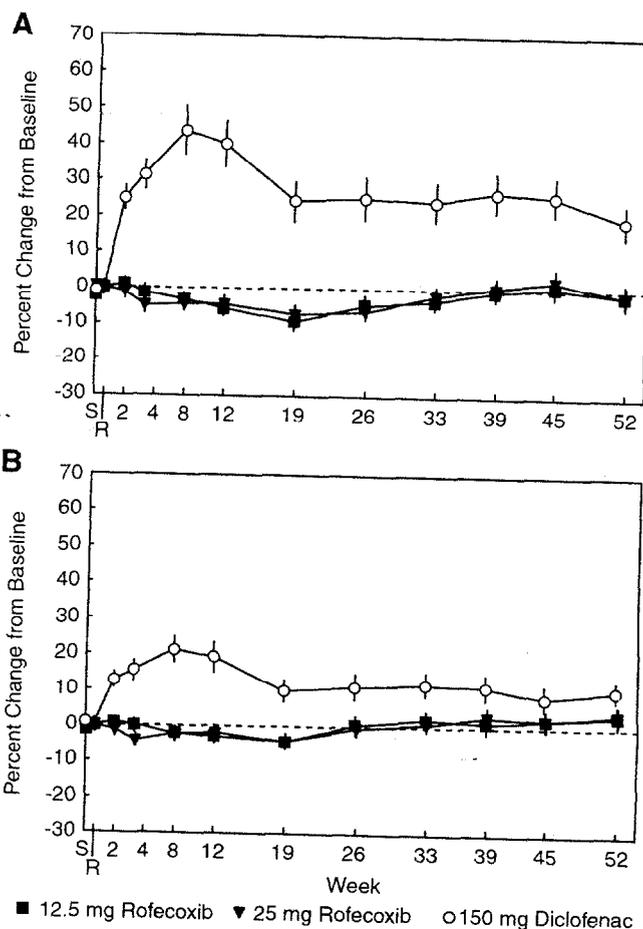
\* Values are the mean ± SD.

edema (reported by the patient) over the year of treatment was similar among the treatment groups (3.9%, 1.9%, and 3.4% in the 12.5-mg rofecoxib, 25-mg rofecoxib, and diclofenac groups, respectively). The clinical significance of these events was minor, since over the entire 1-year duration of the study, only a single patient (12.5-mg rofecoxib group) discontinued therapy because of lower extremity edema and most cases resolved with continuation of treatment. There were 4 episodes of congestive heart failure: 1 in the 12.5-mg rofecoxib group and 3 in the diclofenac group. There were no meaningful changes in blood pressure or serum creatinine levels over the year of treatment among the 3 groups (Table 6). No patient had a clinical episode of acute renal failure.

There were more laboratory adverse events in the diclofenac group compared with the rofecoxib groups, largely due to a greater incidence of increased serum aminotransferase levels. The diclofenac group had pronounced mean changes in alanine and aspartate aminotransferase levels compared with the rofecoxib groups (Figure 3). These elevations caused 11 diclofenac patients (4.1%) to discontinue therapy, compared with none of the patients in the rofecoxib groups.

Because of its action in inhibiting the function of platelets, prolonged therapy with low-dose aspirin reduces the risk of thromboembolic cardiovascular events (35). Although a similar epidemiologic case has not been made for NSAIDs, there has been a theoretical concern that specific inhibition of COX-2, which does not effect platelet function, may not protect the cardiovascular system to the same extent as NSAIDs. In this 1-year study that included patients with cardiovascular risk factors (hypertension in 45%, angina in 3%, hypercholesterolemia in 16%, and diabetes in 7%), the incidence of thromboembolic cardiovascular events, such as myocardial infarction, stroke, transient ischemic attack, and

peripheral arterial occlusions, was numerically lower in the rofecoxib groups (1.5%, 2.3%, and 3.4% in the 12.5-mg



**Figure 3.** Aminotransferase values over time, expressed as the geometric mean percentage of change from baseline. **A**, Alanine aminotransferase; **B**, aspartate aminotransferase. See Figure 1 for definitions.

rofecoxib, 25-mg rofecoxib, and diclofenac groups, respectively).

### DISCUSSION

The discovery of 2 isoforms of COX, the target enzyme inhibited by NSAIDs, poses a number of questions concerning the role of COX-1 and COX-2 in the efficacy and safety of this widely prescribed class of drugs. Previous studies have demonstrated that specific COX-2 inhibitors are efficacious in the treatment of OA, but did not answer the question as to how that efficacy compares with the efficacy of NSAIDs (36).

In this study, the efficacy of rofecoxib was comparable to that of a high dose of the NSAID diclofenac. Predefined clinical comparability criteria were used for the primary analysis because the scientific question of interest was whether rofecoxib had clinical efficacy comparable to that of an NSAID in the treatment of OA. Small statistical differences favoring diclofenac compared with 25 mg of rofecoxib were seen for 2 of the end points: <0.20 Likert units for patient's assessment of response to therapy and physician's assessment of disease status. These differences and the associated 95% CI were well within the clinical comparability bounds prespecified for this study. These bounds are more conservative than those recommended by a panel of expert rheumatologists (31). In addition, 0.2 Likert units is markedly smaller than the recently determined minimal perceptible clinical improvement of 0.5 units for these end points in OA studies (37). Thus, both the 12.5-mg and the 25-mg doses of rofecoxib are clinically comparable by the strict, prespecified comparability criteria to diclofenac for all 3 primary end points.

In addition, the effects of rofecoxib on a variety of the clinical manifestations of OA, as assessed by secondary end points, were comparable to those of diclofenac for all end points. These results were obtained in a representative population of OA patients, and the results were consistent across study joint, age, and sex.

There are several potential limitations to this study. No placebo group was included in the study because of the inability to maintain patients who have painful OA symptoms on a regimen of placebo for 1 year. The treatment responses in this study were markedly similar to those of rofecoxib groups in other placebo-controlled trials that clearly demonstrated significant differences compared with placebo (36,38). In addition, the responses seen with rofecoxib were comparable to those seen with high doses of diclofenac, an

NSAID widely accepted as efficacious in the treatment of OA.

All studies are subject to dropouts, which affect the interpretation of the data. The 43% incidence of discontinuation for this 1-year study was less than that of a long-term study of OA comparing naproxen with acetaminophen (39). When adjusted for duration of exposure, it is lower than the 30–34% discontinuation rate for 12-week OA studies without placebo controls (40,41). The overall incidence of discontinuation was similar among all treatment groups. The effects of dropouts on the results were minimized by employing an intention-to-treat analysis and by not imputing values for patients who discontinued.

Overall, during 1 year of treatment, all treatments were generally well tolerated. It is important to note that no adverse event unique to the specific inhibition of COX-2 was observed in the rofecoxib treatment groups. The overall incidences of adverse events and discontinuations for clinical adverse events were similar among the treatment groups.

The hypothesis of improved GI safety and tolerability for inhibitors that are specific for COX-2 cannot be answered with the results of a single trial. Early published results for rofecoxib and celecoxib demonstrate an improved GI safety profile compared with NSAIDs (42,43). An endoscopic study of OA patients confirmed the significantly improved GI safety profile of rofecoxib in comparison to standard NSAID therapy (28). In that study, patients who received rofecoxib (25 and 50 mg) had significantly fewer endoscopic gastroduodenal ulcers compared with those who received ibuprofen (2.4 gm) over 6 months of treatment (9.6%, 14.7%, and 45.8% for the 25-mg rofecoxib, 50-mg rofecoxib, and ibuprofen groups, respectively). In addition, the incidence of endoscopic gastroduodenal ulcers in the rofecoxib group was equivalent to placebo for the 12-week placebo treatment period.

In the present 1-year study, there were fewer symptomatic ulcers in the combined rofecoxib groups (0.8%) compared with the diclofenac group (1.2%). The numbers of patients in the study were too small to support a conclusion of a decrease in the incidence of PUB events. A combined analysis of all OA clinical studies has been performed and demonstrated a statistically important decrease in PUBs for rofecoxib-treated patients compared with NSAID-treated patients (44). Thus, based both on the endoscopy data and the analysis of clinical PUB events, rofecoxib appears to have a meaningful improvement in GI safety compared with NSAIDs.

Treatment with rofecoxib for 1 year did not have

an effect on serum aminotransferase levels. In contrast, the elevations in serum aminotransferase levels in the diclofenac group were consistent with the published experience (45).

The most common renal effects of NSAIDs attributable to the inhibition of COX are a reduction in glomerular filtration rate (GFR) and reductions in the excretion of sodium, with the potential for fluid retention and edema. The intrarenal distribution and regulation of renal COX-2 by sodium intake suggests a role for this enzyme in renal physiology and in the renal effects of NSAIDs (46,47). It has been previously shown that the acute (24–48 hours postdose) sodium-retaining effect of 50-mg rofecoxib is comparable to that of the NSAID indomethacin (48). This effect resolves over the 14 days of treatment with rofecoxib, in contrast to the persistence of this effect with indomethacin. In addition, rofecoxib did not significantly affect the GFR (48). In this 1-year study, the renal effects of rofecoxib were similar to those of diclofenac, as assessed by spontaneous reports of lower extremity edema. Most of these events resolved while continuing study therapy, and few patients discontinued treatment because of these events. There were no significant effects on the mean diastolic or systolic blood pressure or on serum creatinine levels.

In summary, the specific inhibition of COX-2 with rofecoxib at a dosage of 12.5 mg and 25 mg once daily provided comparable clinical efficacy to that of diclofenac 50 mg 3 times daily in the treatment of OA of the knee and hip. Rofecoxib was generally well tolerated.

#### ACKNOWLEDGMENTS

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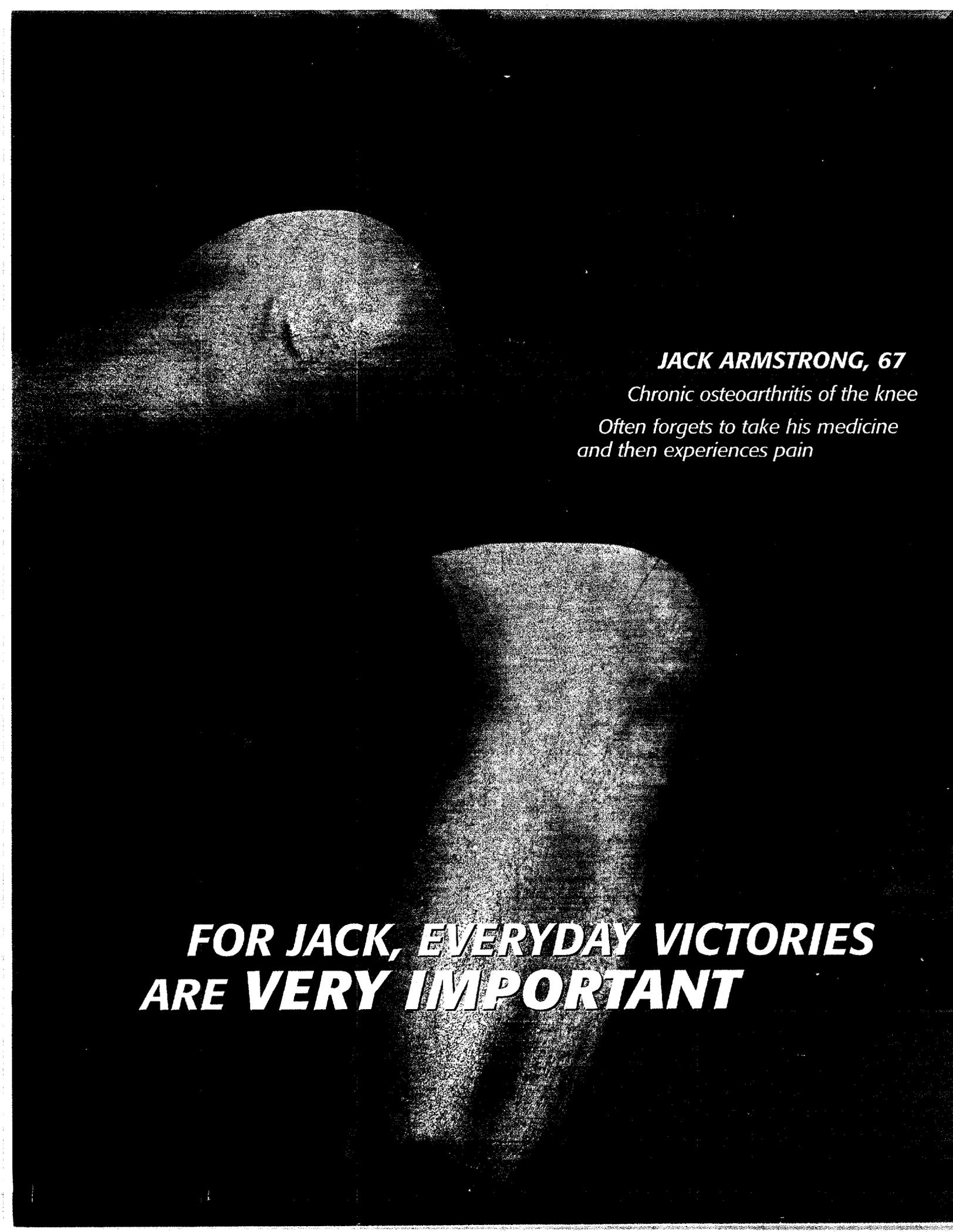
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#### APPENDIX A: THE ROFECOXIB PROTOCOL 035 STUDY GROUP

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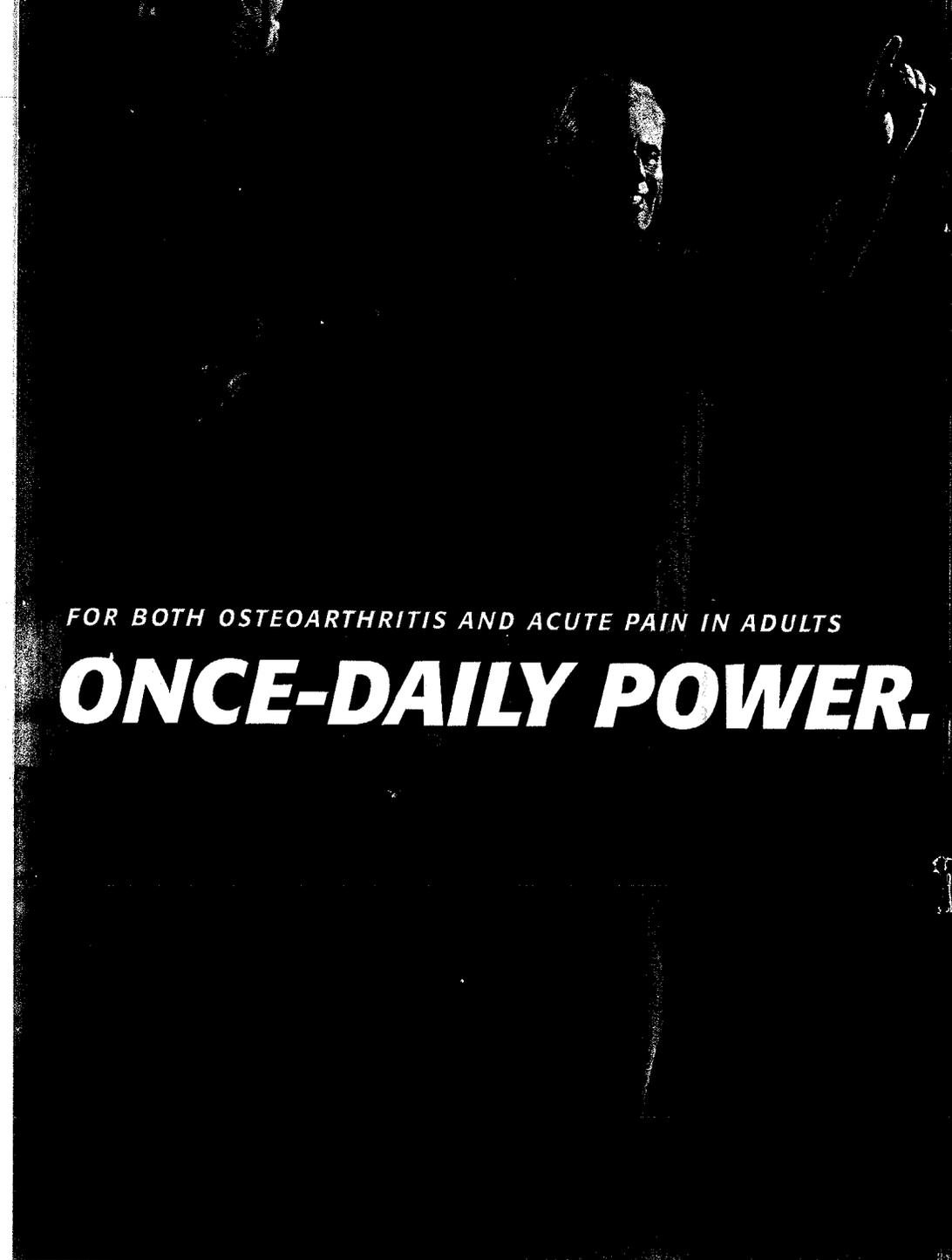


**JACK ARMSTRONG, 67**

*Chronic osteoarthritis of the knee*

*Often forgets to take his medicine  
and then experiences pain*

***FOR JACK, EVERYDAY VICTORIES  
ARE VERY IMPORTANT***



FOR BOTH OSTEOARTHRITIS AND ACUTE PAIN IN ADULTS

**ONCE-DAILY POWER.**

**INDICATED FOR**

- Relief of the signs and symptoms of osteoarthritis (OA).
- Management of acute pain in adults (see CLINICAL STUDIES).
- Treatment of primary dysmenorrhea.

**CONTRAINDICATED IN**

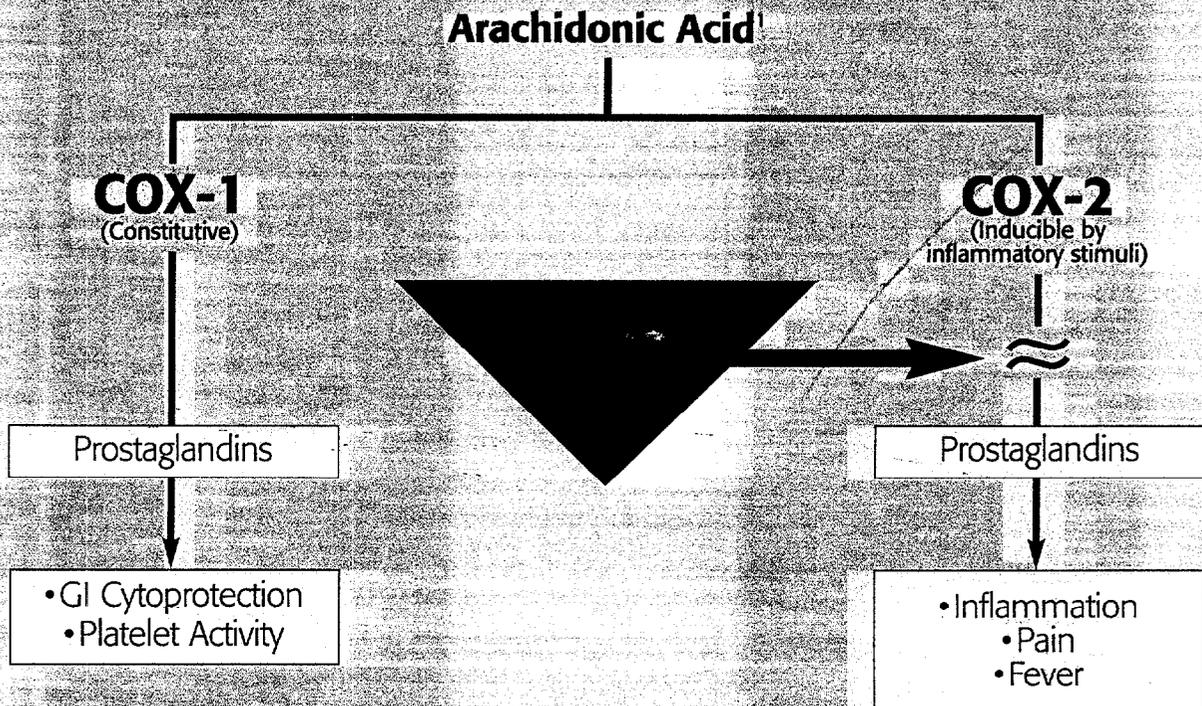
- Patients with known hypersensitivity to rofecoxib or any other component of VIOXX.
- Patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

**NO SULFONAMIDE CONTRAINDICATION**

**STRENGTH. SAFETY. QD SIMPLICITY.**

# INHIBIT COX-2 WITHOUT INHIBITING COX-1

- 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.



- COX-1 is the enzyme primarily responsible for the production of prostaglandins that regulate normal physiologic functions, such as gastric cytoprotection and platelet activity.
- COX-2 is the enzyme primarily responsible for the production of prostaglandins that regulate pain, inflammation, and fever.

# CLINICAL PHARMACOLOGY

**No effect on platelet function or bleeding time in healthy volunteers**

**VIOXX is not a sulfonamide**

- Clinical studies did not exclude patients with a known sulfonamide allergy.

**Not primarily metabolized by the cytochrome P450 system**

- Metabolized primarily by cytosolic enzymes in the liver.
- Drug-interaction studies with rofecoxib have identified potentially significant interactions with rifampin, methotrexate, and warfarin. Standard monitoring should be continued for patients receiving warfarin or methotrexate concomitantly with VIOXX.

## PHARMACOKINETICS

- The steady-state effective half-life was approximately 17 hours.
- Mean oral bioavailability is approximately 93%.
- 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.
- Food effect on the suspension formulation has not been studied.

Before prescribing VIOXX, please read the complete Prescribing Information enclosed in the pocket.

**ONCE DAILY**  
**VIOXX<sup>®</sup>**  
**(rofecoxib)**

# **WITH NSAIDS, SERIOUS UPPER GI ADVERSE EVENTS MAY OCCUR WITHOUT PRIOR GI SYMPTOMS**

- **4 out of 5 patients** who develop a serious upper gastrointestinal (GI) adverse event on NSAID therapy are asymptomatic immediately prior to the event.
- **10 times higher risk** for developing a GI bleed in patients with a prior history of peptic ulcer disease and/or GI bleeding, and who use NSAIDs, than in patients with neither of these risk factors.

## **Patients who may be at higher risk for serious GI events when taking NSAIDs include those with:**

- History of ulcer disease.
- Therapy with anticoagulants.
- Use of oral corticosteroids.
- Longer duration of NSAID therapy.
- Older age.
- Poor general health status.

# **GI EVENT DATA FOR VIOXX: STUDIES OF 6 WEEKS TO 1 YEAR**

- Among 3,357 patients who were treated with VIOXX 12.5 mg, 25 mg, and 50 mg in controlled clinical trials of six weeks' to one year's duration (most were enrolled in six-month or longer studies), a total of four patients experienced a serious upper GI event
  - two patients experienced an upper GI bleed within three months (0.06%)
  - one patient experienced an obstruction within six months
  - one patient experienced an upper GI bleed within 12 months, for a total incidence of 0.12% over one year

**Cumulative Incidence of Serious Clinical Upper GI Events  
In Patients Treated With VIOXX (N=3,357)  
Obstruction and Significant Bleeds**

<b>0-3 Months</b> Number of Patients (%)	<b>0-12 Months</b> Number of Patients (%)
2 (0.06%)	4 (0.12%)

Approximately 23% of these 3,357 patients were in studies that required them to be free of ulcers at study entry. It is unclear if this study population is representative of the general population.

### **IMPORTANT GI RISK INFORMATION**

Serious GI toxicity, such as bleeding, ulceration, and perforation, can occur with or without warning symptoms in patients treated with NSAIDs; these GI events appear to occur in approximately 1% of patients treated for three to six months and in 2% to 4% of patients treated for one year. It is unclear at the present time how these rates apply to VIOXX.

To minimize GI risk, use the lowest effective dose for the shortest possible duration.

**ONCE DAILY**  
**VIOXX<sup>®</sup>**  
**(rofecoxib)**

GI SAFETY

VIOXX

## **GI STUDIES WITH VIOXX® (rofecoxib)**

### **ENDOSCOPIC GI STUDIES INCLUDED PATIENTS AT HIGHER RISK**

- History of perforation, ulcer, or bleed
- Age  $\geq 65$  years
- Baseline gastroduodenal erosions
- Active *Helicobacter pylori* infection
- Patients receiving aspirin were not included in these studies.
- NSAIDs should be prescribed with extreme caution in patients with a prior history of ulcer disease or GI bleeding. Studies have shown that patients with a prior history of peptic ulcer disease and/or GI bleeding, and who use NSAIDs, have a greater than tenfold higher risk for developing a GI bleed than patients with neither of these risk factors.

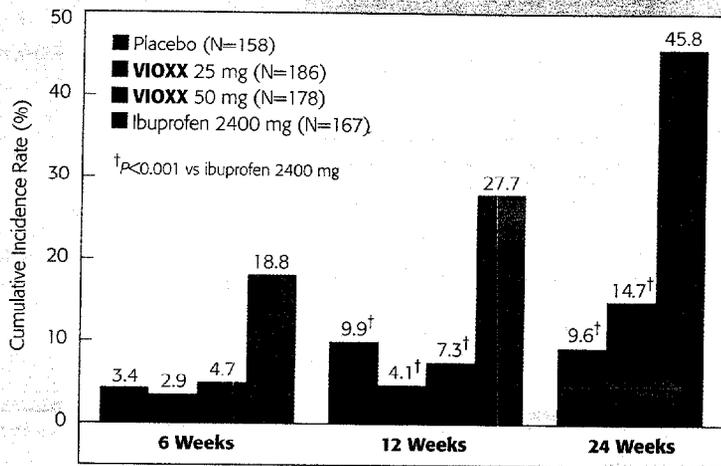
#### **Important considerations for endoscopy studies**

- Serious, clinically significant upper GI bleeding has been observed in patients receiving VIOXX in controlled clinical trials, albeit infrequently.
- Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking VIOXX vs comparator NSAID products have not been performed.

# IN TWO IDENTICAL STUDIES OF OA PATIENTS

## SIGNIFICANTLY FEWER ENDOSCOPIC ULCERS THAN WITH IBUPROFEN

### Cumulative Incidence of Gastroduodenal Ulcers $\geq 3$ mm—U.S. Study\*



\*One of two identical (U.S. and multinational) endoscopy studies, in a total of 1,516 OA patients who had no ulcers at baseline, that 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. Endoscopy was repeated at 6, 12, and 24 weeks. The placebo-treatment group was discontinued at Week 16 by design. The primary endpoint was the cumulative incidence of gastroduodenal ulcer over 12 weeks.

### Endoscopic Gastroduodenal 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

- Incidence rates of ulcers in groups receiving VIOXX did not increase over time — no significant difference between the first 12 weeks and the second 12 weeks of the studies<sup>2</sup>

### Important considerations for endoscopy studies

- The correlation between endoscopic findings and the relative incidence of clinically serious upper GI events that may be observed with different products has not been fully established.
- These studies cannot rule out at least some increase in the rate of endoscopic gastroduodenal ulcers when comparing VIOXX with placebo.

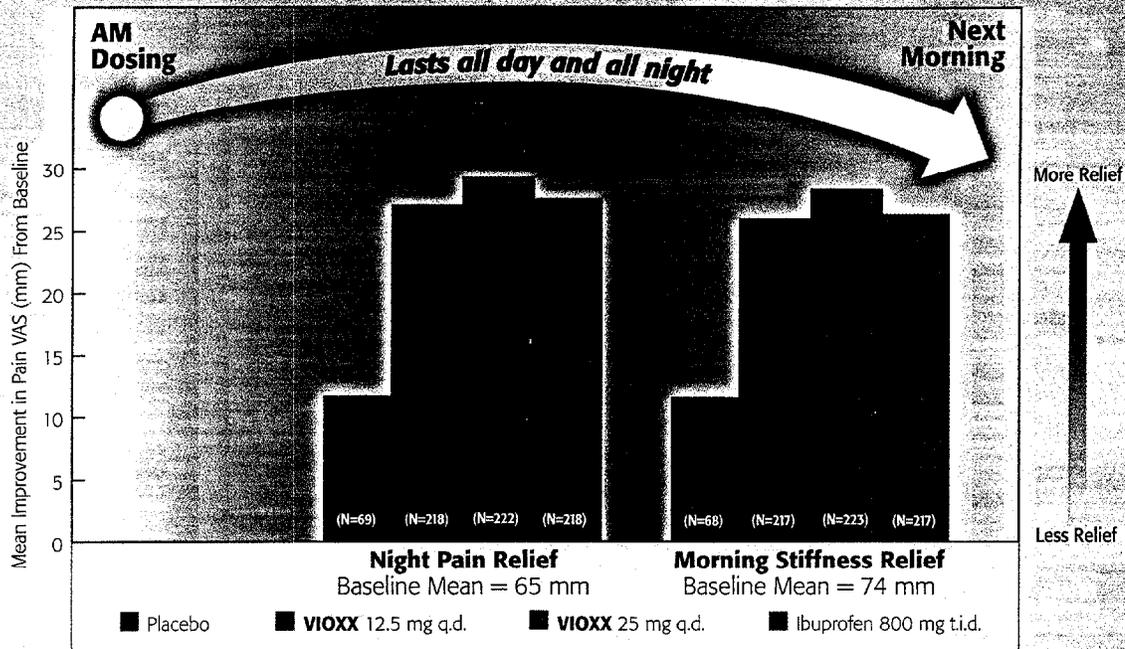
ONCE DAILY

**VIOXX**<sup>®</sup>  
(rofecoxib)

# ONCE-DAILY POWER TO LAST IN OSTEOARTHRITIS

One morning dose provided relief throughout the day and night,  
and upon awakening the next morning

Patient Response Over 6 Weeks\*—WOMAC (0–100-mm Visual Analog Scale [VAS])



$P < 0.001$  for VIOXX vs placebo;  $P = \text{NS}$  for VIOXX vs ibuprofen.

\* Randomized, double-blind, placebo- and active-comparator-controlled, parallel-group study to assess the efficacy and safety of VIOXX q.a.m. dosing (12.5 mg q.d., 25 mg q.d.) vs ibuprofen (800 mg t.i.d.) in patients with OA of the hip or knee.

† The Western Ontario and McMaster Universities (WOMAC) questionnaire was used, which is based on patient's assessment of pain, obtained from a 24-question survey comprised of three subscales: Pain (5 questions), Stiffness (2 questions), and Physical Function (17 questions).

The six-week measurements of "Pain at Night" (WOMAC Question 3) and "Morning Stiffness" (WOMAC Question 6) were measured on a 0–100-mm VAS, in which 0 mm = No Pain/No Stiffness and 100 mm = Extreme Pain/Extreme Stiffness.

- Significant improvement in evening pain and morning stiffness vs placebo ( $P < 0.001$ ) and similar to ibuprofen 2400 mg (800 mg t.i.d.).

**Comparable Efficacy**

VIOXX 12.5 mg or 25 mg once daily	ibuprofen 800 mg three times a day
●	● ● ●

Tablets represented at actual size; 12.5-mg tablet shown.

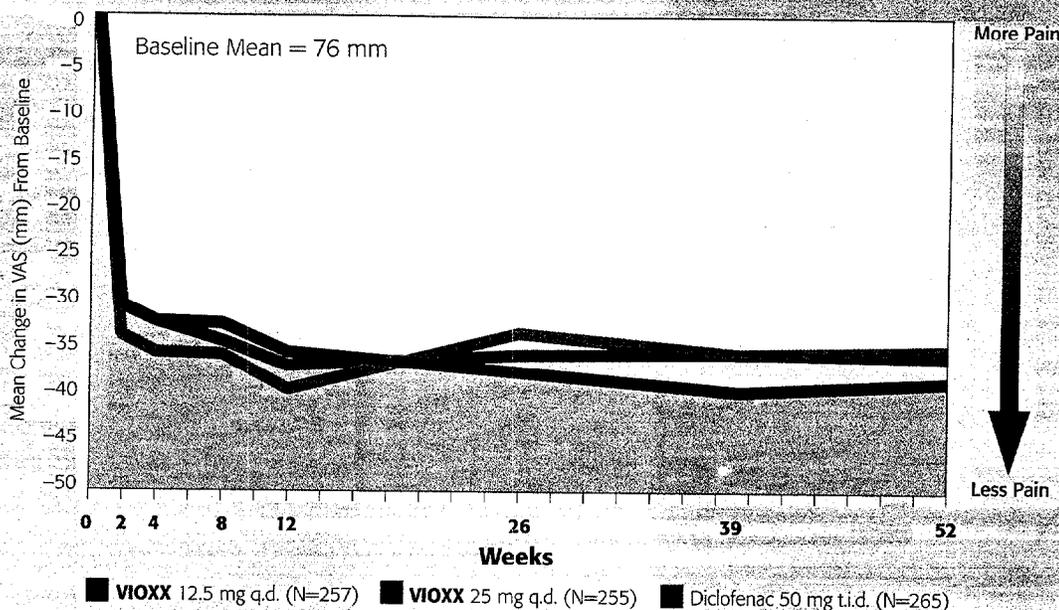
✓ **All clinical trials used q.d. dosing** for all patients receiving VIOXX.

**Common adverse events included** upper respiratory infection (8.5%), diarrhea (6.5%), nausea (5.2%), and hypertension (3.5%).

# IN CHRONIC OA PAIN

## RELIEF DEMONSTRATED IN STUDIES LASTING 1 YEAR

Pain Walking on a Flat Surface\*<sup>4</sup>  
WOMAC<sup>†</sup> (0-100-mm VAS)



\* Randomized, double-blind, active-comparator-controlled, parallel-group study to assess the efficacy and safety of VIOXX (12.5 mg, 25 mg) vs diclofenac 150 mg (50 mg t.i.d.) in patients with pain accompanying OA flare of the hip or knee.

<sup>†</sup> The Western Ontario and McMaster Universities (WOMAC) questionnaire was used, which is based on patient's assessment of pain, obtained from a 24-question survey comprised of three subscales: Pain (5 questions), Stiffness (2 questions), and Physical Function (17 questions).

The primary endpoint, Pain Walking on a Flat Surface (WOMAC Question 1 from the Pain subscale), measured by a 0-100-mm VAS, in which 0 mm = No Pain and 100 mm = Extreme Pain.

- Once-daily VIOXX 12.5 mg and 25 mg were comparable to diclofenac 150 mg (50 mg t.i.d.).
- Patients could receive additional arthritis medications during the last six months of the study.
- VIOXX is not a substitute for aspirin for cardiovascular prophylaxis because it does not affect platelet function.

Before prescribing VIOXX, please read the complete Prescribing Information enclosed in the pocket.

**ONCE DAILY**  
**VIOXX**<sup>®</sup>  
(rofecoxib)

OA EFFICACY

ACUTE PAIN EFFICACY

ELDERLY

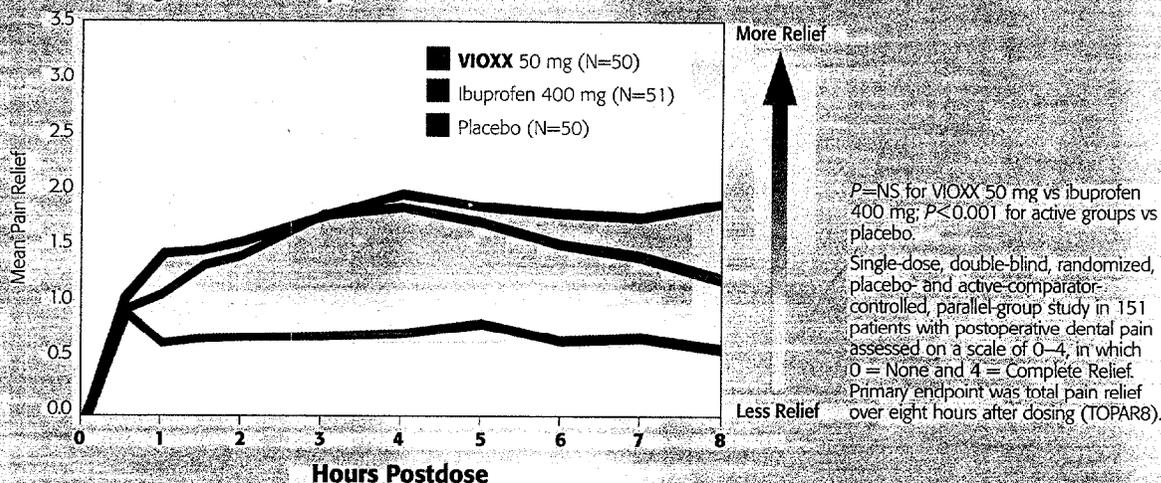
COST/SUMMARY

# FAST ONSET IN ACUTE PAIN IN ADULTS

## Onset of pain relief within 45 minutes in single-dose studies of postoperative dental pain

- The management of acute pain beyond five days has not been studied
  - acute-pain studies were designed to last up to five days

### Postoperative Dental Pain Relief A Single-Dose Study<sup>5</sup>



## Relief of moderate to severe pain with a single, nonnarcotic daily dose

- A single dose of VIOXX 50 mg provided pain relief generally similar to ibuprofen 400 mg, the maximum single dose for analgesia
  - for analgesia, VIOXX 50 mg is dosed once daily, as needed
  - for analgesia, ibuprofen 400 mg can be dosed every four to six hours

**Common adverse events in OA studies included** upper respiratory infection (8.5%), diarrhea (6.5%), nausea (5.2%), and hypertension (3.5%).

The adverse-experience profile in analgesia studies was generally similar to the adverse-experience profile reported in OA studies.

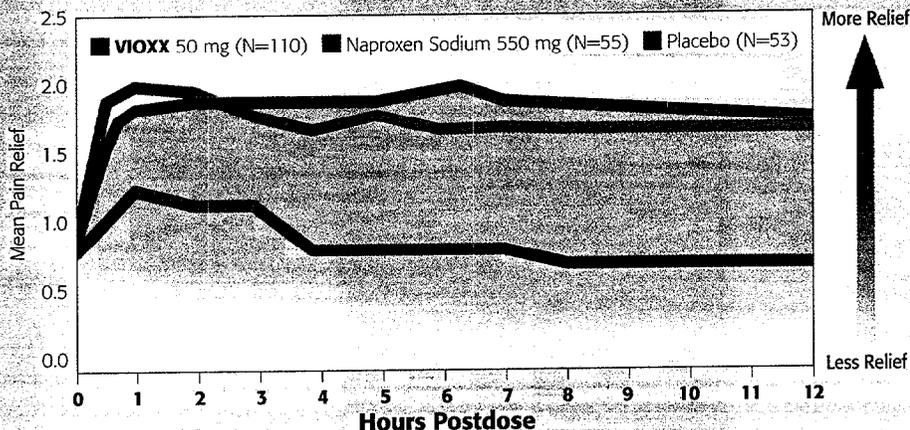
In the postoperative dental pain studies, the following additional adverse experience was reported in  $\geq 2\%$  of patients treated with VIOXX: postdental extraction alveolitis (dry socket).

The general safety profile of VIOXX 50 mg q.d. in OA clinical trials of up to six months (476 patients) was similar to that of VIOXX at the recommended OA doses of 12.5 mg and 25 mg q.d., except for a higher incidence of GI symptoms (abdominal pain, epigastric pain, heartburn, nausea, and vomiting), lower extremity edema (6.3%), and hypertension (8.2%).

# ONCE-DAILY POWER IN ACUTE PAIN IN ADULTS

Pain relief generally similar to naproxen sodium 550 mg

Postorthopedic Surgical Pain<sup>6</sup> (Hip or Knee Replacement)



$P < 0.001$  for VIOXX vs placebo;  
 $P = \text{NS}$  for VIOXX vs naproxen.

Multiple-dose, double-blind, randomized, placebo- and active-comparator-controlled, parallel-group five-day study in 218 patients 18 years of age or older who underwent knee or hip replacement. Postorthopedic surgery improvement in pain relief shown on Day 1 of 5. Pain relief was measured on a scale of 0-4, in which 0 = None and 4 = Complete Relief.

## ✓ VIOXX 50 mg significantly reduced the need for narcotic rescue analgesia over the five-day acute-pain study

- Patients first received VIOXX, on average, 46 hours after surgical procedure (range, 17 to 97 hours).
- Once-daily VIOXX 50 mg was effective in reducing postorthopedic surgical pain over the five days of the study.

## ✓ VIOXX 50 mg: once-daily power consistently demonstrated in all models studied

- Postorthopedic surgical pain.
- Postoperative dental pain.
- Primary dysmenorrhea.

### Selected safety information

There are no studies of VIOXX in pregnant women. VIOXX should be used during pregnancy only if the potential benefit justifies the potential risk. As with other NSAIDs, VIOXX should be avoided in late pregnancy as it may cause premature closure of the ductus arteriosus.

ONCE DAILY  
**VIOXX**<sup>®</sup>  
(rofecoxib)

**SHARON  
BRIGHTMAN,  
42**

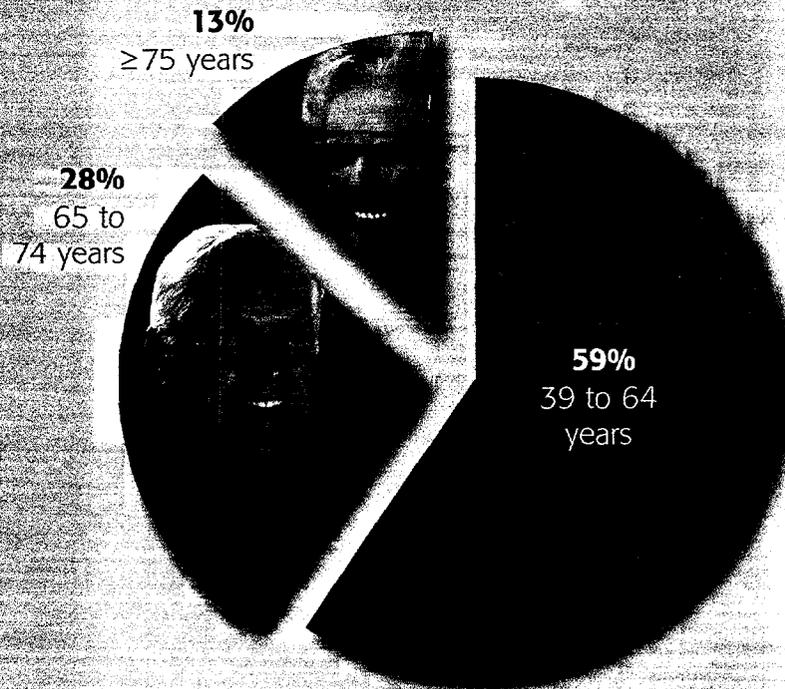
*Acute pain*

# **SAFETY PROFILE IN ELDERLY PATIENTS**

## **OA trials included large numbers of elderly patients**

- 1,455 were  $\geq 65$  years of age.
- 460 of these patients were  $\geq 75$  years of age.

Age Distribution of OA Patients Treated With  
VIOXX<sup>®</sup> in all Clinical Trials



## **No substantial differences in safety were observed between older and younger patients**

- Greater sensitivity in some older patients cannot be ruled out.

### **Selected safety information**

- Dosage adjustment in the elderly is not necessary; however, therapy with VIOXX should be initiated at the lowest recommended dose.
- With NSAIDs, most spontaneous reports of fatal GI events are in elderly or debilitated patients
  - therefore, special care should be taken in treating these patients

# **SAFETY PROFILE SIMILAR IN ELDERLY AND YOUNGER PATIENTS**

## **In a specific six-week study of patients 80 years of age or older**

- 174 OA patients who received VIOXX demonstrated a safety profile similar to that of younger patients.
- As with all NSAIDs, VIOXX should be used with caution in patients with fluid retention, hypertension, or heart failure.

## **ONCE-DAILY DOSE TAKEN WITH OR WITHOUT FOOD**

**VIOXX is not contraindicated in patients with  
sulfonamide allergies**

### **References:**

1. Schwartz JJ et al. Cyclooxygenase-2 inhibition by rofecoxib reverses naturally occurring fever in humans. *Clin Pharmacol Ther*. 1999;65(6):653-660.
2. Laine L et al. A randomized trial comparing the effect of rofecoxib, a cyclooxygenase-2-specific inhibitor, with that of ibuprofen in the gastroduodenal mucosa of patients with osteoarthritis. *Gastroenterology*. 1999;117(4):776-783.
3. Data available on request from Professional Services, WP1-27, Merck & Co., Inc., West Point, PA 19486. Please specify information package DA-VIO5(2).
4. Cannon GW et al. Rofecoxib, a specific inhibitor of cyclooxygenase 2, with clinical efficacy comparable with that of diclofenac sodium: results of a one-year, randomized, clinical trial in patients with osteoarthritis of the knee and hip. *Arthritis Rheum*. 2000; 43(5):978-987.
5. Morrison BW et al. Analgesic efficacy of the cyclooxygenase-2-specific inhibitor rofecoxib in post-dental surgery pain: a randomized, controlled trial. *Clin Ther*. 1999;21(6):943-953.
6. Data available on request from Professional Services, WP1-27, Merck & Co., Inc., West Point, PA 19486. Please specify information package DA-VIO1(2).

### **LIZ GOODWIN, 85**

*OA in multiple joints  
History of sulfonamide allergy  
Has trouble remembering  
medication schedules*



**ONCE DAILY**  
**VIOXX<sup>®</sup>**  
**(rofecoxib)**

# ONE TABLET, ONCE DAILY— ONE PRICE

## Compare cost of therapy with branded NSAIDs in OA

Product	Class	OA Dose	Regimen*	WAC <sup>†</sup>
<b>VIOXX</b>	NSAID	12.5 mg	12.5-mg tablet q.d.	<b>\$2.02</b>
		25 mg	25-mg tablet q.d.	<b>\$2.02</b>
Celebrex (celecoxib)	NSAID	200 mg	200-mg capsule q.d.	<b>\$2.02</b>
			or 100-mg capsule b.i.d.	<b>\$2.38</b>
Arthrotec (diclofenac sodium and misoprostol)	NSAID/ prostaglandin analog	Arthrotec 50 (50 mg diclofenac sodium/200 µg misoprostol)	50-mg tablet t.i.d.	<b>\$3.66</b>
Daypro (oxaprozin)	NSAID	1200 mg	Two 600-mg caplets q.d.	<b>\$2.56</b>
Relafen (nabumetone)	NSAID	1000 mg	Two 500-mg tablets q.d.	<b>\$2.04</b>
		1500 mg	Two 750-mg tablets q.d.	<b>\$2.40</b>
		2000 mg	Two 750-mg tablets + one 500-mg tablet q.d.	<b>\$3.42</b>
Voltaren-XR (diclofenac sodium)	NSAID	100 mg	100-mg tablet q.d.	<b>\$2.60</b>

\* As recommended in the DOSAGE AND ADMINISTRATION section of the respective product labels.

<sup>†</sup> Wholesale Acquisition Cost (WAC) is the manufacturer's catalog price charged to wholesalers.

VIOXX is a registered trademark of Merck & Co., Inc. Other brands listed are trademarks of their respective owners and are not trademarks of Merck & Co., Inc.

- Referenced prices are derived from published price lists (Source: PriceProbe™ Version 6.1, Copyright 1998, April 2000, First DataBank/Hearst Corp.) and do not necessarily reflect actual prices paid by consumers or dispensers.
- The above price comparison does not establish that the products have comparable efficacy.
- Lower acquisition cost alone does not necessarily reflect a cost advantage in the outcome of the condition treated because there are other variables that affect relative costs.

### Selected safety information

- Safety and effectiveness in pediatric patients below the age of 18 years have not been evaluated.
- Serious renal and hepatic reactions have been reported with NSAID use.
- VIOXX is not recommended in patients with moderate or severe hepatic insufficiency or in patients with advanced kidney disease.

# ONCE-DAILY POWER FROM THE ONLY COX-2-TARGETED AGENT

- ✓ Not contraindicated in patients with a history of sulfonamide allergies
- ✓ Always once daily for all indications
- ✓ Indicated for acute pain in adults
- ✓ Indicated for primary dysmenorrhea
- ✓ Priced the same for either OA dose<sup>1</sup>
- ✓ Available as an oral suspension
- ✓ Reduced the need for narcotic rescue analgesia in a postorthopedic surgical pain study<sup>6</sup>

## Selected safety information

- 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.
- Drug-interaction studies with VIOXX have identified potentially significant interactions with rifampin, methotrexate, and warfarin.
  - Standard monitoring should be continued for patients receiving methotrexate concomitantly with VIOXX.
  - Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing therapy with VIOXX in patients receiving warfarin or similar agents, since these patients are at increased risk of bleeding complications. In postmarketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin.

**ONCE DAILY**  
**VIOXX**<sup>®</sup>  
(rofecoxib)

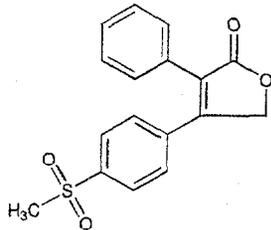


# VIOXX®

(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 C<sub>17</sub>H<sub>14</sub>O<sub>4</sub>S, 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.

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 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<sub>max</sub>) following a single 25-mg dose were 3286 (±843) ng·hr/mL and 207 (±111) ng/mL, respectively. Both C<sub>max</sub> 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<sub>max</sub> 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<sub>max</sub>), as assessed in nine pharmacokinetic studies, is 2 to 3 hours. Individual T<sub>max</sub> values in these studies ranged between 2 to 9 hours. This may not reflect rate of absorption as T<sub>max</sub> may occur as a secondary peak in some individuals. With multiple dosing, steady-state conditions are reached by Day 4. The AUC<sub>0-24hr</sub> and C<sub>max</sub> 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 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<sub>max</sub>) or extent of absorption (AUC) of rofecoxib when VIOXX tablets were taken with a high fat meal. The time to peak plasma concentration (T<sub>max</sub>), 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<sub>max</sub> 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<sub>ss</sub>) 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 its

## VIOXX® (rofecoxib tablets and oral suspension)

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., 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.

#### Renal Insufficiency

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

*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.

## 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

## VIOXX® (rofecoxib tablets and oral suspension)

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. 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).

### Special Studies

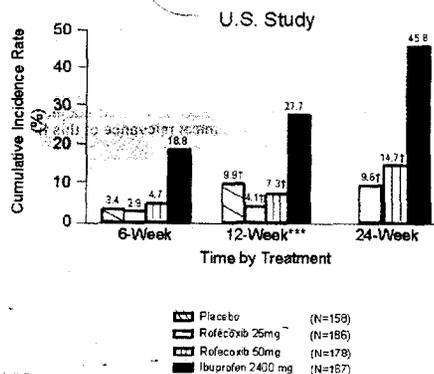
#### Upper Endoscopy in Patients with Osteoarthritis

Two identical (U.S. and Multinational) endoscopy studies in a total of 1516 patients were conducted to compare the percentage of patients who developed endoscopically detectable gastroduodenal ulcers with VIOXX 25 mg daily or 50 mg daily, ibuprofen 2400 mg daily, or placebo. 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.

Figure 1

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



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

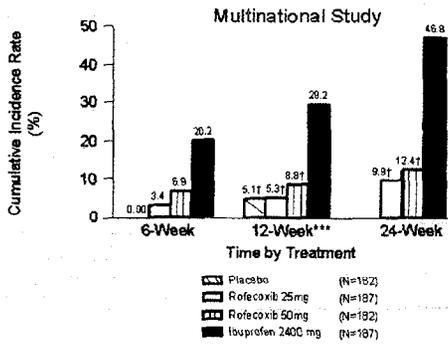
\*\*\* The primary endpoint was the cumulative incidence of gastroduodenal ulcer at 12 weeks.

TABLE 1  
Endoscopic Gastroduodenal 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  $\geq 3$ mm\*\* (Intention-to-Treat)**



† p < 0.001 versus ibuprofen 2400 mg

\*\* Results of analyses using a  $\geq 3$  mm gastroduodenal ulcer endpoint were consistent.

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

**TABLE 2**  
**Endoscopic Gastroduodenal Ulcers at 12 weeks**  
**Multinational Study**

Treatment Group	Number of Patients with Ulcers/Total Number of Patients	Cumulative Incidence Rate	Ratio of Rates vs. Placebo	95% CI on Ratio of Rates
Placebo	5/182	5.1%	1.0	—
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

The correlation between findings of endoscopic studies, and the relative incidence of clinically serious upper GI events that may be observed with different products, has not been fully established. 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*). Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking VIOXX versus comparator NSAID products have not been performed.

#### 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  $^{51}\text{Cr}$ -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. Similarly, bleeding time was not altered in a single dose study with 500 or 1000 mg of VIOXX. There was no inhibition of *ex vivo* arachidonic acid- or collagen-induced platelet aggregation with 12.5, 25, and 50 mg of VIOXX.

#### 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.

#### 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, anaphylactoid-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-inflam-

matory 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.

It is unclear, at the present time, how the above rates apply to VIOXX (see CLINICAL STUDIES, *Special Studies, Upper Endoscopy in Patients with Osteoarthritis*). Among 3357 patients who received VIOXX in controlled clinical trials of 6-weeks to one-year duration (most were enrolled in six-month or longer studies) at a daily dose of 12.5 mg to 50 mg, a total of 4 patients experienced a serious upper GI event, using protocol-derived criteria. Two patients experienced an upper GI bleed within three months (at day 62 and 87, respectively) (0.06%). One additional patient experienced an obstruction within six months (Day 130) and the remaining patient developed an upper GI bleed within 12 months (Day 322) (0.12%). Approximately 23% of these 3357 patients were in studies that required them to be free of ulcers at study entry. It is unclear if this study population is representative of the general population. Prospective, long-term studies required to compare the incidence of serious, clinically significant upper GI adverse events in patients taking VIOXX vs comparator NSAID products have not been performed.

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.

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

#### Anaphylactoid Reactions

As with NSAIDs in general, anaphylactoid reactions have occurred in patients without known prior exposure to VIOXX. In post-marketing experience, rare cases of 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.

#### Advanced Renal Disease

No safety information is available regarding the use of VIOXX in patients with advanced kidney disease. Therefore, treatment with VIOXX is not recommended in these patients. If VIOXX therapy must be initiated, close monitoring of the patient's kidney function is advisable (see PRECAUTIONS, *Renal 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 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. Clinical trials with VIOXX at daily doses of 12.5 and 25 mg have shown renal effects (e.g., hypertension, 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.)

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*).

#### 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 CLINICAL STUDIES, *Special Studies, Platelets*).

#### Fluid Retention and Edema

Fluid retention and edema have been observed in some patients taking VIOXX (see ADVERSE REACTIONS). VIOXX should be used with caution, and should be introduced at the lowest recommended dose in patients with fluid retention, hypertension, or heart failure.

#### 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. 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 promptly report signs or symptoms of gastrointestinal ulceration or bleeding, skin rash, unexplained weight gain, or edema 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.

**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 TXB<sub>2</sub> generation in clotting blood. VIOXX is not a substitute for aspirin for cardiovascular prophylaxis.

**Cimetidine:** Co-administration with high doses of cimetidine (800 mg twice daily) increased the C<sub>max</sub> of rofecoxib by 21%, the AUC<sub>0-120hr</sub> by 23% and the t<sub>1/2</sub> 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. 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<sub>0-24hr</sub> 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.

**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 prednisone or prednisolone.

**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 AUC<sub>0-24</sub>) and in male and female rats given oral doses up to 8 mg/kg (approximately 8- and 2-fold the human exposure at 25 and 50 mg daily based on AUC<sub>0-24</sub>) 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 *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 AUC<sub>0-24</sub>) and rofe-

coxib 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<sub>0-24</sub>).

**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 AUC<sub>0-24</sub>). 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<sub>0-24</sub>). 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 AUC<sub>0-24</sub> 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<sub>0-24</sub>). 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<sub>0-24</sub>). 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 AUC<sub>0-24</sub> 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 represents an approximate 18- and 6-fold human exposure at 25 and 50 mg based on AUC<sub>0-24</sub>. 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). 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 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 (N = 783)	VIOXX 12.5 or 25 mg daily (N = 2829)	Ibuprofen 2400 mg daily (N = 847)	Diclofenac 150 mg daily (N = 498)
<b>Body As A Whole/Site Unspecified</b>				
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
<b>Cardiovascular System</b>				
Hypertension	1.3	3.5	3.0	1.6
<b>Digestive System</b>				
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
<b>Eyes, Ears, Nose, And Throat</b>				
Sinusitis	2.0	2.7	1.8	2.4
<b>Musculoskeletal System</b>				
Back Pain	1.9	2.5	1.4	2.8
<b>Nervous System</b>				
Headache	7.5	4.7	6.1	8.0
<b>Respiratory System</b>				
Bronchitis	0.9	2.0	1.4	3.2
<b>Urogenital System</b>				
Urinary Tract Infection	2.7	2.8	2.5	3.6

The general safety profile of VIOXX 50 mg QD in OA clinical trials of up to 6 months (476 patients) was similar to that of VIOXX at the recommended OA doses of 12.5 and 25 mg QD, except for a higher incidence of gastrointestinal symptoms (abdominal pain, epigastric pain, heartburn, nausea and vomiting), lower extremity edema (6.3%) and hypertension (8.2%).

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, crills, 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 heart beat, 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, dyspepsia, 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

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heart failure, deep venous thrombosis, myocardial infarction, 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, intestinal obstruction, pancreatitis.

**Hemic and lymphatic:** lymphoma.

**Immune System:** anaphylactoid reaction, angioedema.

**Nervous System:** aseptic meningitis.

**Psychiatric:** hallucinations.

**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.

**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.

VIOXX® (rofecoxib tablets and oral suspension)

**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.

**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.

VIOXX® (rofecoxib tablets and oral suspension)

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 100  
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. 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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# ONCE-DAILY POWER. VERY VIOXX.

Anytime, day or night, with or without food,  
for all indications

**Osteoarthritis (same price for either dose)**

 Starting dose: 12.5 mg q.d.  
12.5 mg q.d.

 Some patients may receive additional benefit by increasing the dose to 25 mg q.d., the maximum recommended dose.  
25 mg q.d.

**Acute Pain in Adults or Primary Dysmenorrhea**

 Initial dose: 50 mg q.d.  
Subsequent doses of 50 mg q.d. as needed.  
50 mg q.d. Use of VIOXX for more than five days in management of pain has not been studied.

Tablets shown at actual size



Available in strawberry-flavored 12.5 mg/5 mL and 25 mg/5 mL oral suspension

Therapy should be initiated at the lowest recommended dose.

## Selected safety information

- Serious GI toxicity can occur with or without warning symptoms with NSAIDs.
- There are no studies of VIOXX in pregnant women. VIOXX should be used during pregnancy only if the potential benefit justifies the potential risk. As with other NSAIDs, VIOXX should be avoided in late pregnancy as it may cause premature closure of the ductus arteriosus.
- Serious renal and hepatic reactions have been reported with NSAID use.
- VIOXX is not recommended in patients with moderate or severe hepatic insufficiency or in patients with advanced kidney disease.

Before prescribing VIOXX, please read the complete Prescribing Information enclosed in the pocket.

**STRENGTH. SAFETY. QD SIMPLICITY.**



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