NDA 21-042: VIOXX™ Tablets
NDA 21-052: VIOXX™ Oral Suspension
(Rofecoxib)

VIOXX™ **G**astrointestinal **O**utcomes **R**esearch Study (**VIGOR**)

FDA Advisory Committee Background Information

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Introduction and Organization of the Document

Rofecoxib (VIOXX™[1]) is a selective cyclooxygenase-2 (COX-2) inhibitor that is approved for the relief of the signs and symptoms of osteoarthritis (OA) (at chronic doses of 12.5 to 25 mg daily) and for the treatment of acute pain and dysmenorrhea (at a dose of 50 mg daily in studies up to 5 days). This document presents the VIOXX™ Gastrointestinal Outcomes Research (VIGOR) study, a single, large clinical outcomes trial designed to provide definitive proof of the improved gastrointestinal (GI) safety of rofecoxib compared with a standard, nonselective NSAID and to secure a labeling change for rofecoxib that eliminates the NSAID-class GI *Warning* and adds a description of the GI effects.

The "COX-2 hypothesis" proposes that the anti-inflammatory and analgesic effects of nonsteroidal anti-inflammatory drugs (NSAIDs) are due to inhibition of COX-2 while the GI toxicity of NSAIDs is due to inhibition of COX-1. It predicts that a selective COX-2 inhibitor should have efficacy equivalent to NSAIDs but with an improved safety profile in the GI tract. The original NDA for rofecoxib contained clinical data consistent with the COX-2 hypothesis that established the COX-2 selectivity of rofecoxib, efficacy comparable to NSAIDs for OA, acute pain and dysmenorrhea and improved GI safety versus nonspecific NSAIDs measured by a number of surrogate and clinically significant endpoints.

The results of the recently completed VIGOR trial demonstrated that rofecoxib 50 mg, at 2 times the highest recommended chronic dose, was associated with a 54 to 62% reduction in the risk of clinically significant GI events compared to naproxen 500 mg twice daily, its most common dose, and less than the maximum recommended dose. Additional general safety information from VIGOR was consistent with the approved U.S. product circular for rofecoxib. These results further confirm the COX-2 hypothesis and support product labeling that distinguishes rofecoxib from nonselective NSAIDs.

The organization of the document after this Introduction is as follows:

Synopsis

Section 1. Overview

The "COX-2 Hypothesis" and data establishing the COX-2 selectivity of rofecoxib are briefly reviewed.

Section 2. The VIOXX™ Gastrointestinal Outcomes Research Study: GI Safety Results

VIGOR is described, in detail, and the GI safety results are presented.

[1] VIOXX is a trademark of Merck & Co., Inc., Whitehouse Station, New Jersey, U.S.A.

Section 3. Review of the Rofecoxib Gastrointestinal (GI) Safety Program Prior to VIGOR

The extensive GI safety program for rofecoxib that was conducted prior to VIGOR is reviewed with particular attention to how the program complements the VIGOR results.

Section 4. General Safety of Rofecoxib

The general safety profile (other than GI safety) of rofecoxib is reviewed with special emphasis on the data from VIGOR.

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SYNOPSIS

Section 1. Overview

Nonsteroidal anti-inflammatory drugs (NSAIDs) produce their therapeutic anti-inflammatory and analgesic effects by inhibiting cyclooxygenase (COX). There are 2 known isoforms of COX with distinct patterns of expression. COX-1 is constitutively expressed in many tissues; it is the only isoform expressed in platelets and is the isoform constitutively expressed in the mucosa of the gastrointestinal (GI) tract. COX-2 is the isoform induced by proliferative or pro-inflammatory stimuli and is expressed at sites of inflammation. COX-2 has also been found constitutively in the normal human kidney. Conventional NSAIDs such as ibuprofen, diclofenac, naproxen, nabumetone, indomethacin and aspirin are nonselective, inhibiting both COX-1 and COX-2 isoforms (nonselective NSAIDs).

The appreciation that COX-1 and COX-2 have different patterns of expression led to the "COX-2 hypothesis". There are 4 key components of the COX-2 hypothesis as currently understood. First, the hypothesis proposed that COX-2 is the isoenzyme important for generating prostaglandins that mediate inflammation, pain, and fever. Second, the COX-2 hypothesis proposed that COX-1 produces prostaglandins important for "housekeeping" functions such as maintaining GI epithelial integrity. Third, given the pattern of expression of COX-2 in the human kidney, the COX-2 hypothesis proposed that COX-2 was involved in renal salt and water handling and in the regulation of blood pressure. Fourth, the COX-2 hypothesis proposed that COX-1 was the isoform that is responsible for normal platelet function. In addition, it was subsequently recognized that COX-2 can participate in the production of prostacyclin (PGI_2), a vasodilatory prostanoid that is an inhibitor of platelet aggregation. The COX-2 hypothesis predicts, therefore, that a selective inhibitor of COX-2 should have the anti-inflammatory and analgesic efficacy of nonselective NSAIDs without the risk of NSAID gastropathy but with renal/blood pressure effects similar to nonselective NSAIDs. Also, a selective inhibitor of COX-2 would not possess the antiplatelet effects of nonselective NSAIDs and may have, theoretically, a prothrombotic effect.

Rofecoxib is a selective inhibitor of COX-2 that is approved for the relief of the signs and symptoms of osteoarthritis (OA) at chronic doses of 12.5 to 25 mg per day and for the treatment of acute pain and dysmenorrhea at a dose of 50 mg per day in studies of up to 5 days. In the original NDA, the COX-2 selectivity of rofecoxib was demonstrated in numerous preclinical models and in human studies using ex vivo assays for COX-1 and COX-2 activity. Rofecoxib inhibited COX-2, in a dose-dependent fashion, with nearly complete inhibition at daily doses of 100 mg. In contrast, at daily doses of up to 375 mg for 12 days and at single doses of up to 1000 mg, rofecoxib demonstrated no inhibition of COX-1. The lack of in vivo COX-1 inhibition by rofecoxib was further demonstrated by assaying endogenous COX activity in gastric biopsy samples (the target tissue for NSAID

gastropathy) obtained from healthy subjects treated with placebo and either rofecoxib or naproxen. Rofecoxib showed no inhibition of gastric COX-1 activity whereas naproxen inhibited gastric COX-1 by ~65 to 70%.

The original NDA for rofecoxib contained an array of clinical studies which supported the prediction of the COX-2 hypothesis; that is, rofecoxib demonstrated therapeutic efficacy comparable to nonselective NSAIDs with markedly reduced GI toxicity. The data on the reduction of GI toxicity from the original NDA is briefly reviewed in Section 3 because it complements and corroborates the definitive results of the VIOXX™ GI Outcomes Research Study (VIGOR) which is the centerpiece of the supplemental New Drug Application that is currently under review by the Agency (Section 2) The lack of antiplatelet effects and possible prothrombotic effects of a selective COX-2 inhibitor prompted MRL to implement, prior to VIGOR, several initiatives designed to evaluate these issues. The results of these initiatives are discussed in Section 4.

Section 2. The VIOXX™ Gastrointestinal Outcomes Research Study (VIGOR): GI Safety Results

VIGOR was an active-comparator-controlled, parallel-group, double-blind, multicenter study designed to provide definitive proof of the improved GI safety of rofecoxib compared with a standard, nonselective NSAID and to secure a labeling change for rofecoxib that eliminates the NSAID-class GI *Warning*. Eight thousand seventy-six patients (8076) with rheumatoid arthritis (RA) were randomized to rofecoxib 50 mg once a day (2 to 4 times the recommended dose for the treatment of OA and anticipated to be 2 times the recommended dose for the treatment of RA), or naproxen 500 mg twice a day (the most commonly used dose for RA and less than the maximum recommended dose) for a median duration of 9 months. The primary endpoint of this study was the occurrence of gastroduodenal perforations, gastric outlet obstructions, symptomatic gastroduodenal ulcers, and upper gastrointestinal bleeding (clinical upper GI events) and a key secondary endpoint was the occurrence of complicated clinical upper GI events (perforations, obstructions and major upper GI bleeds). All events identified by the investigators as potential clinical upper GI events were adjudicated as either confirmed or not by a blinded, independent Case Review Committee (CRC) using prespecified criteria.

At study conclusion, of the 8076 patients evenly divided between rofecoxib and naproxen, 177 had clinical upper GI events confirmed by the CRC. Among the 177 patients with confirmed clinical upper GI events, 53 had events that were adjudicated as complicated clinical upper GI events. The risk of development of a confirmed clinical upper GI event was 54% lower in patients treated with rofecoxib than in patients treated with naproxen ($p<0.001$). The risk of development of a confirmed, complicated clinical upper GI event was 57% lower in patients treated with rofecoxib than in patients treated with naproxen ($p=0.005$). The risk of upper or lower GI bleeds was 62% lower in patients treated with rofecoxib than in patients treated with naproxen ($p<0.001$). The relative risk was constant over time for all endpoints.

Prespecified per-protocol and sensitivity analyses confirmed the results and attested to their robustness. Results for all secondary and exploratory endpoints supported the primary endpoint. There were consistent treatment effects for rofecoxib and naproxen on the primary endpoint among various subgroups of patients classified according to demographic parameters and the presence or absence of risk factors which predispose patients to the development of clinical upper GI events. These data demonstrated consistent treatment effects across all subgroups.

In order to validate the GI safety comparison in VIGOR several standard RA efficacy measures were incorporated to establish that rofecoxib and naproxen provided similar efficacy in this study. Although this trial was not designed to establish efficacy of rofecoxib in the treatment of RA (e.g., non-flare design), there were no differences between treatments in their effects on the efficacy endpoints.

Section 3. Review of the Rofecoxib Gastrointestinal (GI) Safety Program Prior to VIGOR

An extensive GI safety program had been conducted with rofecoxib before initiating VIGOR and was reported in the original NDA. Rofecoxib was shown to be similar to placebo and significantly less GI toxic than nonselective NSAIDs in studies of the incidence of endoscopic gastroduodenal erosions, abnormal intestinal permeability and microscopic fecal blood loss in healthy subjects. Longer term (24-week) endoscopic surveillance studies in OA patients extended these results by demonstrating that treatment with rofecoxib 25 or 50 mg daily was associated with a significantly lower incidence of ulcers than treatment with ibuprofen 2400 mg daily. Finally, a combined analysis of clinical upper GI events in all 8 Phase IIb/III OA studies demonstrated that there was a 55% reduction in risk of clinical upper GI events in OA patients taking rofecoxib (mean dose 24.7 mg) versus the combined nonselective NSAID group (ibuprofen, diclofenac, and nabumetone) ($p=0.006$). This GI safety benefit mirrors that observed in RA patients in VIGOR (54% risk reduction). Together, the results conclusively support the hypothesis that NSAID gastropathy is associated with the inhibition of COX-1 by nonselective NSAIDs and that the use of the selective COX-2 inhibitor, rofecoxib, substantially reduces the risk of NSAID-type GI damage.

Section 4. General Safety of Rofecoxib

The primary safety data in the original NDA for rofecoxib were derived from the study of approximately 3600 OA patients exposed to 12.5-, 25-, or 50-mg doses participating in Phase II and III studies. Overall, therapy with rofecoxib was found to be generally well-tolerated. As predicted by the COX-2 hypothesis, adverse experiences associated with rofecoxib represent a subset of those described for the nonselective NSAIDs and the incidence of these non-GI events with rofecoxib is similar to the incidence with nonselective NSAIDs dosed at comparable points on their efficacy dose-response curves.

The VIGOR study used rofecoxib 50 mg daily (2 times the maximum recommended chronic dose of rofecoxib) and naproxen 1000 mg daily (less than the maximum

recommended chronic dose of naproxen). Despite this, the general adverse experience profile of rofecoxib in VIGOR was consistent with the previous experience in the OA studies at comparable doses and with the current approved U.S. Product Circular for rofecoxib (see Appendix 3).

Adverse experiences due to COX-2 inhibition (i.e., edema and hypertension) were of special interest and were specifically evaluated in VIGOR. These adverse experiences are mechanism-based and dose-related. The incidence of lower-extremity edema in VIGOR (4.0% in the rofecoxib group) was lower than in the studies with rofecoxib 50 mg described in the current U.S. Product Circular (6.3%). The incidence of hypertension adverse experiences in the rofecoxib group in VIGOR (8.5% in the rofecoxib group) was similar to the incidence in the studies with rofecoxib 50 mg described in the current U.S. Product Circular (8.2%).

One finding in VIGOR that required further exploration was a significantly lower incidence of thrombotic cardiovascular serious adverse experiences in the naproxen group compared to the rofecoxib group. In a process established prior to the initiation of VIGOR, cardiovascular events during VIGOR were adjudicated as thrombotic events by an independent cardiovascular event committee established for the entire rofecoxib clinical development program. The rate of confirmed thrombotic cardiovascular serious adverse experiences was 0.70 per 100 patient-years for the naproxen group and 1.67 per 100 patient-years for the rofecoxib group. Thus, therapy with naproxen was associated with a 58% lower risk for the development of thrombotic events due primarily to a lower incidence of myocardial infarctions.

The decreased incidence of cardiovascular events in the naproxen group compared to the rofecoxib group could be explained by either a cardioprotective effect of naproxen or a prothrombotic effect of rofecoxib. These alternatives were explored in several ways. Clinical pharmacology studies documented an aspirin-like effect of naproxen throughout its dosing interval on measures of platelet function. Other nonselective NSAIDs studied had less potent and/or less sustained effects on platelet function. The incidences of cardiovascular events in several other clinical studies with rofecoxib, were evaluated. These included: all 8 completed Phase IIb/III trials involving 5435 OA patients exposed to rofecoxib, placebo, or several non-naproxen nonselective NSAIDs; 2 ongoing trials which have enrolled approximately 2000 patients with early Alzheimers Disease who are evenly randomized to rofecoxib or placebo; and a formal meta-analysis of all available Phase IIb through Phase V controlled clinical trials from the rofecoxib development program including VIGOR. The analyses of these data did not display a significant difference in the incidence of thrombotic cardiovascular events between the rofecoxib groups and the various comparator groups except in the VIGOR comparison to naproxen.

Additionally, in VIGOR, naproxen therapy was associated with an increased incidence of ecchymosis and epistaxis relative to rofecoxib therapy. These results provide independent support that naproxen has clinically important antiplatelet effects.

The totality of the data support the hypothesis that the disparity in cardiovascular event incidences between the treatment groups in VIGOR was due to naproxen having conveyed an antiplatelet, cardioprotective effect in VIGOR. Rofecoxib has no antiplatelet activity. The difference in antiplatelet activity between nonselective NSAIDs with potent and sustained COX-1 inhibiting activity and selective COX-2 inhibitors may be of clinical significance in patients at risk for thromboembolic events. Therefore, patients who require low-dose aspirin therapy for cardiovascular prophylaxis should continue on aspirin during therapy with rofecoxib.

Section 5. Summary

Rofecoxib has been shown to have efficacy similar to nonselective NSAIDs in OA, acute analgesia and dysmenorrhea and is approved for use in these patient populations. Both the VIGOR trial and the combined Phase IIb/III OA studies demonstrated that rofecoxib is associated with a 54 to 62% lower risk of clinical upper GI events, complicated clinical upper GI events, and GI bleeds compared to nonselective NSAIDs. Rofecoxib demonstrated consistency of effect in reducing the risk of these events in all subgroups analyzed.

The aggregate of data from the rofecoxib development program in close to 30,000 patients supports the general tolerability and safety and, in particular, the cardiovascular safety of rofecoxib. The VIGOR results, which revealed significantly fewer thrombotic cardiovascular events on naproxen, are most consistent with naproxen having provided a relative cardioprotective benefit to patients at risk for these events.

Rofecoxib represents a clinically important improvement over nonselective NSAIDs by markedly reducing the risk of clinical upper GI events.

Section 6. Overall Conclusions

- The results of VIGOR confirm that rofecoxib has a GI safety profile superior to nonselective NSAIDs. These results support deletion of the NSAID-class GI *Warning* from the rofecoxib U.S. Product Circular and a description of the GI effects in the label. This will serve to appropriately distinguish rofecoxib from nonselective NSAIDs.
- The results of VIGOR confirm the general safety profile of rofecoxib as presented in the currently approved U.S. Product Circular.

1. Overview

1.1 Burden of Disease and Risks/Benefits of NSAIDs

Living with arthritis is a challenge that is faced daily by as many as 15% of persons in industrialized nations [1 to 3]. In the population over 55 years of age, the prevalence of arthritis is reported to be as high as 44% [1; 3]. Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most commonly used treatment for arthritis [4; 5]. Population studies in several industrialized countries indicate that 10 to 20% of the elderly (≥65 years old) have a current or recent NSAID prescription [6]. The number who use nonprescription NSAIDs is likely higher [4; 6].

The major toxicity of nonselective NSAIDs, NSAID gastropathy, can lead to upper GI ulceration and clinically significant GI complications including gastroduodenal perforations, symptomatic ulcers with or without gastric outlet obstruction, and upper GI bleeding [7 to 9]. These events have been reported in 2 to 4% of patients taking nonselective NSAIDs for a year [10; 11]. Ulcers associated with nonselective NSAIDs are frequently asymptomatic with a complication (perforation, obstruction, significant bleeding) as the initial presentation in 80% of cases [12 to 15].

NSAID gastropathy represents a major public health problem in the U.S., accounting for approximately 100,000 hospitalizations and 15,000 deaths annually [8]. Thus, NSAID gastropathy is the 15th most common cause of death in the United States. Factoring in morbidity and cost for care, the estimated cost of NSAID gastropathy in the United States alone exceeds $2 billion [16].

Because of this toxicity, all NSAIDs carry a class *Warning* in their product labels about the risks of serious GI events. An NSAID with significantly reduced GI toxicity would represent an important advance over conventional therapies.

1.2 The COX-2 Hypothesis and Risks/Benefits of COX-2 Selective NSAIDs

NSAIDs produce their effects by inhibiting the cyclooxygenase (COX) enzymes [17]. The COX enzymes control the rate-limiting step in the cellular production of the prostanoids prostaglandin D_2 (PGD_2), PGE_2, PGI_2 (prostacyclin), $PGF_{2\alpha}$ and thromboxane A_2 (TXA_2) [18]. There are 2 known COX isoforms [19; 20] with distinct patterns of expression. COX-1 is expressed constitutively in many tissues; it is the only isoform expressed in platelets and is the isoform constitutively expressed in the mucosa of the gastrointestinal (GI) tract [21; 22]. COX-2 is the inducible isoform; it is induced to high level expression by proliferative or pro-inflammatory stimuli [19; 21; 23; 24] and is expressed at sites of inflammation including rheumatoid synovium [23] and chondrocytes from patients with osteoarthritis (OA) [25; 26]. COX-2 is also present at other locations. Especially relevant is the finding that COX-2 is expressed constitutively in the kidney [27; 28] and its expression is upregulated in conditions associated with intravascular volume depletion [29].

The appreciation that COX-2 has a different pattern of expression and is involved in different functions than COX-1 led to what has been called the "COX-2 hypothesis" [30]. Conventional nonselective NSAIDs such as ibuprofen, diclofenac, nabumetone, naproxen, indomethacin, and aspirin inhibit both COX-1 and COX-2 isoforms within their clinical dose range [31]. The COX-2 hypothesis proposed that a highly selective COX-2 inhibitor would be superior to nonselective NSAIDs in certain critical ways and similar in other ways [32].

There are four key components of the COX-2 hypothesis as currently understood. First, the hypothesis proposed that COX-2 is the isoenzyme important for generating prostaglandins that mediate inflammation, pain, and fever. It predicted that a highly selective COX-2 inhibitor would be as effective in treating these symptoms of disease as a nonselective NSAID (i.e., an inhibitor of both COX-1 and COX-2) [33]. Second, the COX-2 hypothesis proposed that COX-1 produces prostaglandins important for "housekeeping" functions such as maintaining GI epithelial integrity [33; 34]. It predicted that a highly selective COX-2 inhibitor would have a substantially improved GI safety profile compared with a nonselective NSAID. Third, given the pattern of expression of COX-2 in the human kidney [27], the COX-2 hypothesis proposed that COX-2 was involved in renal salt and water handling and in the regulation of blood pressure. It predicted that the renal/vascular effects of highly selective COX-2 inhibitors would be similar to nonselective NSAIDs.

The fourth component of the COX-2 hypothesis concerned the effects of COX-1 and COX-2 on platelet function. The COX-2 hypothesis proposed that COX-1 was the isoform involved in the production of platelet thromboxane, a vasoconstrictive prostanoid that is a promoter of platelet aggregation. It predicted that a highly-selective COX-2 inhibitor would not affect platelet function and would not have antiplatelet effects like those attributable to certain nonselective NSAIDs. In addition, it was subsequently recognized that COX-2 can participate in the production of prostacyclin (PGI_2), a vasodilatory prostanoid that is an inhibitor of platelet aggregation [35; 36]. The ability of a highly selective COX-2 inhibitor to inhibit the synthesis of systemic prostacyclin but not platelet thromboxane raised the theoretical possibility that a highly selective COX-2 inhibitor might alter the balance between these 2 prostanoids and might therefore be prothrombotic [35].

Based on the prediction that a highly selective COX-2 inhibitor would have a substantially improved GI safety profile compared with a nonselective NSAID, Merck Research Laboratories (MRL) initiated a drug development program for a selective COX-2 inhibitor. Rofecoxib (VIOXX™) is a result of that program.

1.3 Studies Supporting the COX-2 Selectivity of Rofecoxib

Rofecoxib is a selective inhibitor of COX-2 at doses well in excess of the clinical range. The COX-2 selectivity of rofecoxib was demonstrated in numerous preclinical models and in human studies using ex vivo assays for COX-1 activity (generation of platelet thromboxane during clotting of whole blood) and COX-2 (induction of monocyte PGE_2

by bacterial lipopolysaccharide [LPS]). As presented in the original New Drug Application (NDA), nearly complete COX-2 inhibition was achieved with 100-mg daily doses of rofecoxib. Furthermore, at daily doses of up to 375 mg for 12 days and at single doses up to 1000 mg, rofecoxib demonstrated no significant inhibition of COX-1.

Importantly, the absence of in vivo COX-1 inhibition by rofecoxib was further demonstrated by assaying endogenous COX activity in gastric biopsy samples obtained from healthy subjects treated with placebo and either rofecoxib or naproxen. COX-1 is the dominant (and the only constitutive) isoform present in normal gastric mucosa. Rofecoxib 25 mg daily and, in a subsequent study, 50 mg daily [37] were compared to naproxen 500 mg twice daily. In both studies, there was no inhibition of gastric COX-1 activity compared with baseline with rofecoxib whereas naproxen inhibited gastric COX-1 activity by approximately 65 to 70%. Thus, there is evidence that rofecoxib is COX-2 selective not only systemically but also in the target organ for the major toxicity of NSAIDs.

1.4 The Rofecoxib Development Program

The rofecoxib development program investigated all key components of the COX-2 hypothesis discussed above: efficacy in relieving pain and inflammation, GI safety, renal/vascular safety, and effects related to platelet function and thrombosis.

Rofecoxib is approved for the relief of the signs and symptoms of osteoarthritis and for the treatment of acute pain and dysmenorrhea. The preclinical program and the OA and analgesia clinical development programs presented in the original NDA demonstrated that rofecoxib is an effective anti-inflammatory and analgesic agent. In 6-week and 1-year studies, rofecoxib 12.5 and 25 mg daily were superior to placebo and similar to nonselective NSAIDs in relieving the signs and symptoms of OA. In studies for up to 5 days, rofecoxib 50 mg daily was effective in treating acute pain and dysmenorrhea.

The GI safety program for rofecoxib presented in the original NDA showed that rofecoxib was associated with significantly less GI toxicity than nonselective NSAIDs. An extensive clinical GI safety program had been conducted and included fecal blood loss, GI permeability, and surveillance endoscopy studies, as well as a combined analysis of clinical upper GI events in OA patients. The VIOXX™ GI Outcomes Research Study (VIGOR) described in this document was initiated in Jan-1999 to provide definitive proof of the improved GI safety of rofecoxib compared with a standard, nonselective NSAID and to secure a labeling change for rofecoxib that eliminates the NSAID-class GI *Warning*.

With regard to non-GI safety, rofecoxib therapy was shown to be associated with renal/vascular adverse effects (hypertension and edema) at an incidence similar to that observed with nonselective NSAIDs, as predicted by the COX-2 hypothesis. These are reported in the approved rofecoxib product circular (Appendix 3).

The original NDA also presented studies that examined the effect of rofecoxib therapy on platelet function. As would be predicted for a COX-2 selective inhibitor, therapy with

rofecoxib does not inhibit platelet function. Studies also demonstrated that rofecoxib does not interfere with the ability of aspirin to inhibit platelet function. The approved rofecoxib product circular states that rofecoxib is not a substitute for aspirin for cardiovascular prophylaxis.

As alluded to earlier, selective COX-2 inhibitors decrease the systemic synthesis of prostacyclin without inhibiting platelet thromboxane [35; 36]. These data raised the theoretical possibility that a highly selective COX-2 inhibitor might alter the balance between these 2 prostanoids and might be prothrombotic. Alternatively, nonselective inhibitors of COX-1 and COX-2 with potent and sustained antiplatelet activity might be cardioprotective. To investigate these possibilities, MRL implemented 2 initiatives prior to the start of VIGOR. First, MRL reviewed the incidence of thrombotic cardiovascular serious adverse experiences throughout the rofecoxib OA development program. This review, previously presented to this committee in Apr-1999, demonstrated that the incidence of thrombotic cardiovascular serious adverse experiences was similar in patients taking rofecoxib, placebo, or the nonselective NSAIDs ibuprofen, diclofenac, and nabumetone. Second, MRL initiated in the second quarter of 1998 a Cardiovascular Adjudication Standard Operating Procedure (Adjudication SOP) for the Post Phase III OA rofecoxib development program. The purpose of the Adjudication SOP was to further evaluate whether there were any differences in the incidence of thrombotic cardiovascular serious adverse experiences during chronic therapy with rofecoxib versus nonselective NSAIDs or placebo. All MRL clinical trials that were initiated in or after the second quarter, 1998, including VIGOR, were to have data on thrombotic cardiovascular serious adverse experiences collected as part of the Adjudication SOP.

1.5 VIGOR: The VIOXX™ GI Outcomes Research Study

VIGOR was a single, large outcomes study designed to definitively evaluate the GI safety advantage of rofecoxib, a selective COX-2 inhibitor, over naproxen, a nonselective inhibitor of COX-1 and COX-2. VIGOR demonstrated that, relative to naproxen, rofecoxib at 2 to 4 times the recommended dose in OA and twice the anticipated dose for RA, is associated with a 54 to 62% reduction in the risk of clinically significant GI events (clinical upper GI events, complicated upper GI events, and all GI bleeds; see Table 1, Section 2.2 for definitions of terms). Additional general safety information from VIGOR is consistent with the OA studies and with the approved U.S. product circular for rofecoxib.

One finding in VIGOR that required further exploration was a significantly lower incidence of thrombotic cardiovascular serious adverse experiences in the naproxen treatment group compared with the rofecoxib group. In contrast, there was no statistically significant difference in the incidence of thrombotic cardiovascular serious adverse experiences between the rofecoxib and nonselective NSAID (ibuprofen, diclofenac, and nabumetone) groups in the OA studies presented in the original NDA. The cardiovascular results of VIGOR could not, by themselves, distinguish between a protective, antiplatelet effect of naproxen due to its COX-1 inhibitory effects or a

prothrombotic effect of rofecoxib. Therefore, additional data were analyzed. Clinical pharmacology studies demonstrated that naproxen inhibits platelet function to an extent similar to that which is reported for aspirin whereas ibuprofen and diclofenac have less pronounced and/or less sustained antiplatelet effects. Consistent with its selectivity for COX-2, rofecoxib does not inhibit platelet COX-1 or platelet function. An ongoing review of cardiovascular outcomes data from other MRL clinical studies and a formal meta-analysis involving over 28,000 patients across rofecoxib Phase IIb to Phase V clinical studies indicated that the risk of thrombotic cardiovascular events is similar in patients taking rofecoxib, patients taking placebo, and patients taking certain nonselective NSAIDs (e.g., ibuprofen, diclofenac, or nabumetone). Thus, it appeared that the cardiovascular findings of VIGOR were different from cardiovascular findings in other studies in the rofecoxib clinical program (trials that did not use naproxen as a comparator for rofecoxib). Taking the results of the clinical pharmacology and clinical research studies for rofecoxib together, the unique cardiovascular findings of VIGOR are most consistent with naproxen having provided a cardioprotective antiplatelet effect.

Overall, the results of the rofecoxib development program confirm the enhanced GI safety of rofecoxib as predicted by the COX-2 hypothesis and demonstrate that COX-1 inhibition is the major mechanism by which nonselective NSAIDs cause gastropathy. The results of VIGOR conclusively demonstrate this point and support deletion of the NSAID-class GI *Warning* from the rofecoxib U.S. Product Circular and a description of the GI effects in the label. This will serve to appropriately distinguish rofecoxib from nonselective NSAIDs. COX-2 inhibitors are similar to nonselective NSAIDs in their renal/vascular effects and the approved rofecoxib product circular reflects this fact. The general safety results of VIGOR are consistent with the approved rofecoxib product circular. Finally, although COX-2 selective inhibitors do not appear to be prothrombotic, they also do not have antiplatelet effects. The difference in antiplatelet activity between nonselective NSAIDs with potent and sustained COX-1 inhibiting activity and selective COX-2 inhibitors may be of clinical significance in patients at risk for thromboembolic events. The results of VIGOR emphasize the existing labeling statement that rofecoxib is not a substitute for aspirin for cardiovascular prophylaxis. It is recommended that patients who require low-dose aspirin therapy for cardiovascular prophylaxis should continue on aspirin during therapy with rofecoxib.

2. The VIOXX™ Gastrointestinal Outcomes Research Study (VIGOR): GI Safety Results

2.1 GI Safety Program Overview—Phase II to III OA Program and VIGOR

The rofecoxib GI safety program was developed to explore the mechanisms for reduced toxicity and to determine, using specific outcomes measures, if the theoretical advantage of selective COX-2 inhibition translated into a clinical benefit for patients. As presented in the original NDA, an extensive GI safety program had been conducted. Rofecoxib was shown to be similar to placebo and significantly improved in comparison to nonselective NSAIDs with regard to the incidence of endoscopically detected gastroduodenal erosions in healthy subjects and comparable to placebo and significantly improved in comparison to nonselective NSAIDs with regard to the induction of fecal blood loss and intestinal permeability. Longer term endoscopic surveillance studies in OA patients extended these results and confirmed that the incidence of endoscopically detected ulcers at 12 and 24 weeks in patients taking rofecoxib 25 mg or 50 mg was significantly less than in patients taking ibuprofen 2400 mg daily. Finally, a combined analysis of GI outcomes (upper GI perforations, symptomatic ulcers, obstructions, or bleeds; clinical upper GI events, see Section 2.2, Table 1) in all 8 Phase IIb/III OA studies demonstrated that there was an approximate 55% reduction in risk of clinical upper GI events in OA patients taking rofecoxib (mean dose 24.7 mg) versus the combined nonselective NSAID group (ibuprofen, diclofenac, and nabumetone). The results of these studies are presented in Section 3.

Based on discussions with regulatory agencies including the U.S. FDA, VIGOR was designed to provide definitive evidence of the improved GI safety of rofecoxib compared with a standard, nonselective NSAID and to support labeling changes for rofecoxib consistent with this enhanced GI profile. Specifically, the goals of VIGOR were to: (1) confirm the reduction of clinical upper GI events for patients taking rofecoxib relative to nonselective NSAIDs that was seen in the prespecified combined analysis of all Phase IIb/III OA studies; (2) demonstrate convincingly that rofecoxib is associated with a significant reduction of complicated upper GI events (see Section 2.2, Table 1) relative to nonselective NSAIDs; and (3) more precisely estimate the magnitude of risk reduction. VIGOR was conducted in RA patients, a population that typically utilizes chronic NSAID therapy, appears to be at high risk for the development of NSAID-related GI toxicity, and in whom the superior GI safety of selective COX-2 inhibitor therapy had not already been established.

The purpose of VIGOR was to provide conclusive evidence of the improved GI safety of rofecoxib compared with a standard, nonselective NSAID. VIGOR was a single, large, multinational, clinical GI outcomes study that included RA patients at high risk for developing significant GI toxicity. Identified risk factors for significant NSAID-related GI toxicity include: duration of therapy, concurrent use of corticosteroids, increasing age, greater arthritis severity, and previous history of a clinical upper GI event [7; 16; 38]. VIGOR, which assessed the GI safety of 50 mg rofecoxib (2 to 4 times the recommended

dose for the treatment of OA and anticipated to be 2 times the recommended dose for the treatment of RA), included patients with each of these risk factors. Consequently, the results of this study are applicable to a broad range of patients requiring chronic treatment with NSAIDs.

The GI safety results of VIGOR are presented in this section of the document along with efficacy measures in RA that were used to validate the selection of doses of rofecoxib and naproxen. The general safety results from VIGOR are presented below in Sections 4.2 and 4.3.

2.2 VIGOR–Design

VIGOR was an active-comparator-controlled, parallel-group, double-blind, multicenter study conducted under in-house blinding procedures. Patients with RA who met entry criteria were randomized to rofecoxib 50 mg once a day or naproxen 500 mg twice a day. Patient allocation was stratified according to whether the patient had a prior history of a clinical upper GI event.

In VIGOR, patients were allowed to use their usual disease-modifying agents (e.g., methotrexate or gold) and/or corticosteroid therapy. However, patients were excluded from the study if they chronically used medication that might confound the analysis of clinical upper GI events. Thus, patients were to be excluded if they required aspirin or other antiplatelet therapy for cardiovascular prophylaxis and were not to stop taking these medications in order to participate in the study. Patients were also excluded if they required therapy with or had recently used proton pump inhibitors, misoprostol, sucralfate, or H_2 blockers at doses indicated for the treatment of ulcers, or if they required therapy with warfarin or heparin.

The primary endpoint of this study was the occurrence of confirmed gastroduodenal perforations, ulcer-related gastric outlet obstructions, symptomatic gastroduodenal ulcers, and upper gastrointestinal bleeding (confirmed clinical upper GI events, Table 1) and a key secondary endpoint was the occurrence of confirmed, complicated upper GI events (i.e., a subset of upper GI events that included perforations, obstructions, and major upper GI bleeds, Table 1; see Appendix 1 for more precise Endpoint Definitions and Adjudication Criteria). Additional secondary endpoints were the occurrence of confirmed plus unconfirmed clinical upper GI events and confirmed plus unconfirmed, complicated upper GI events. An exploratory endpoint was the occurrence of any GI bleed (see Section 2.4.1.4).

Table 1

Nomenclature for Events Described in This Document

Term	Definition
Clinical Upper GI Event	Gastroduodenal Perforation, symptomatic gastroduodenal Ulcer (with or without obstruction), or upper GI Bleed. Note: This is the same as what has been called "PUB".
Complicated Upper GI Event	Gastroduodenal perforation, gastric outlet obstruction due to an ulcer, or a major upper GI bleed (see adjudication criteria in Appendix for specific criteria). Note: This is the same as what has been called "complicated PUB".
Confirmed [Term]	An event that was confirmed by an independent Case Review Committee. The specific diagnosis was assigned by the Case Review Committee.

All events identified by the investigators as potential clinical upper GI events were adjudicated by a blinded Case Review Committee (CRC). The CRC consisted of 3 voting clinicians (2 gastroenterologists and 1 general internist) with expertise in the diagnosis of endpoints and in the conduct of clinical trials. The voting members did not include employees of Merck. No member of the CRC was an investigator for this study, or was directly involved in any way in the conduct of the study. The blinded CRC was assisted in administrative matters by Merck personnel blinded to treatment allocation. The CRC independently classified all potential clinical upper GI events as either confirmed or unconfirmed and either complicated or uncomplicated according to predefined criteria (See Appendix 1 for Endpoint Definitions and Adjudication Criteria). The CRC could also adjudicate an event as "not an upper GI event" if, by majority opinion, the potential endpoint did not involve the upper GI tract as defined (e.g., a case reported as an upper GI bleed by the investigator was determined by the committee to be a lower GI bleed based on case documentation.)

The study conduct was overseen by a blinded Steering Committee. The Steering Committee consisted of non-Merck specialists in the field of epidemiology, rheumatology, gastroenterology, internal medicine, and biostatistics. The blinded Merck Clinical Monitor and a blinded Merck Statistician were also members of the Steering Committee.

Unblinded results of interim safety analyses were reviewed by a Data and Safety Monitoring Board (DSMB). The members of the Board were independent of Merck Research Laboratories and clinical investigators participating in this trial, and did not

have any other involvement in the study, nor any relation to study participants. An unblinded Merck statistician who was excluded from active participation in the study provided the DSMB with the safety analyses. The DSMB was responsible for the safety and integrity of the trial on an ongoing basis.

The duration of VIGOR was both time and event driven. The study was to terminate after a minimum of 120 patients experienced confirmed clinical upper GI events, 40 patients experienced confirmed, complicated upper GI events, and the study had run at least 6 months from the date of last patient randomized.

2.2.1 Clinical Considerations in the Design of VIGOR

2.2.1.1 Rationale for the Choice of Patient Population in VIGOR

The convincing GI safety results from the MRL OA studies precluded a long-term GI outcomes clinical trial in the OA patient population for ethical reasons. However, the GI safety of rofecoxib had not been evaluated in patients with RA.

In addition to the above considerations, RA patients have been noted to be at increased risk for developing a clinical upper GI event compared to patients with OA [16]. Independent risk factors in RA patients for the development of a clinical upper GI event include chronic corticosteroid use, chronic high-dose nonselective NSAID use, and degree of disability [7; 16]. Thus, performing VIGOR in RA patients would be a rigorous test of the GI safety of rofecoxib and extend the Phase IIb/III GI safety findings to a different patient population.

Lastly, because the majority of patients with RA use NSAIDs chronically, exposing RA patients to rofecoxib or a nonselective NSAID comparator for a prolonged period of time would be consistent with clinical practice.

2.2.1.2 Rationale for Selection of Comparator Agent and Dose

Among the possible nonselective NSAID comparators, naproxen was chosen because, in many countries, it is the most commonly used NSAID for the relief of the signs and symptoms of RA [39]. Additionally, because patients with RA often have complicated medical regimens, it was important to simplify and to choose an NSAID comparator which was given at most twice daily. Furthermore, in the previous rofecoxib studies in OA patients, diclofenac, ibuprofen, and nabumetone served as the nonselective NSAID comparators. Therefore, the use of naproxen in VIGOR provided comparative GI safety data against a different nonselective, dual COX-1/COX-2 inhibitor. Furthermore, naproxen is representative of the nonselective NSAID class with regard to the risk of clinical upper GI events. In a meta-analysis by Gabriel et al., the odds ratio of complicated upper GI events for naproxen users versus non-NSAID users was 2.84 (CI, 1.68, 4.82) whereas the odds ratio for users of any nonselective NSAID versus non-NSAID users was 2.74 [5].

In the United States, the recommended dose of naproxen for the treatment of RA in adults is 500 to 1000 mg per day. However, the dose may be increased up to a maximum of

1500 mg per day when a higher level of activity is required. Naproxen 500 mg twice daily is the most commonly used dose for the treatment of RA and therefore was the dose used in VIGOR.

In order to rigorously evaluate the GI safety hypothesis, VIGOR compared a dose of naproxen less than the maximal approved dose with a dose of rofecoxib above the approved dose for chronic use. The dose of rofecoxib used in VIGOR was 50 mg daily. Fifty milligrams is 2 to 4 times the chronic dose approved for marketed use in the treatment of OA (12.5 mg or 25 mg once daily). Rofecoxib 50 mg is also twice the anticipated chronic dose for the treatment of RA. Data from a Phase IIb RA study has demonstrated that 25 mg of rofecoxib provides efficacy similar to 50 mg rofecoxib [40]. Recently unblinded data from the Phase III RA program, not yet reviewed by FDA, confirm these results.

Pharmacokinetic data demonstrate that systemic exposure to rofecoxib is proportional to dose over the 12.5-mg to 100-mg dose range and is similar across populations regardless of gender, age, or race. Thus, the design of VIGOR may even be considered as biased against rofecoxib by using less than the maximum approved dose of naproxen compared to a dose of rofecoxib that is 2 times greater and associated with twice the systemic exposure than the maximum approved dose. In summary, the choice of 50 mg rofecoxib ensured that the safety of the drug was studied at a dose that is anticipated to be higher than the maximum used dose for the treatment of both OA and RA, providing rigorous testing of the GI safety of rofecoxib.

2.2.2 Statistical Considerations in the Design of VIGOR

The prespecified Data Analysis Plan (DAP) approved by the Steering Committee and the DSMB identified a modified intention-to-treat paradigm as the primary analysis. All patients randomized were included based upon their randomized treatment assignment. The primary time frame for the analysis of clinical upper GI event incidence included all events starting at the time of randomization and extended up until the date of either completion for the study or the date of early discontinuation plus a 14-day follow-up period during which patients were requested not to resume non-protocol NSAID therapy. This assured adequate washout of the study agents and ensured that events occurring during this time period were not confounded by non-protocol NSAID use. The modified intention-to-treat approach only differs from an intention-to-treat approach by the exclusion of events past the 14-day follow-up period and up to trial termination in patients who discontinued early. All patients with early discontinuation from the study were followed for possible clinical upper GI events up until the time the study was terminated, making an intention-to-treat analysis possible. However, because an intention-to-treat analysis would include events potentially confounded by post-study treatment, the intention-to-treat analysis was used as a sensitivity analysis whereas the modified intention-to-treat was primary (see Section 2.4.1.5 Per-Protocol and Sensitivity Analyses). Both intention-to-treat approaches provide that all patients be analyzed in the groups they were randomized into, regardless of whether they complied with the

specified protocol. Therefore, in both intention-to-treat approaches, the risk of creating bias by excluding patients or events is minimized and the integrity of the results is maintained.

There was one planned interim analysis of the GI safety results which occurred after 66 clinical upper GI events had occurred. This was reviewed by the DSMB and a decision to continue the trial was made by the DSMB according to predefined stopping rules described in the Data Analysis Plan (DAP).

For the primary endpoint in the final analysis, an α spending function was used to adjust the quoted p-values and confidence intervals to reflect the interim analysis. For other analyses, the nominal p-values were employed.

2.3 VIGOR–Demographics and Populations Analyzed

The VIGOR study enrolled and randomized 8076 RA patients at 301 sites worldwide. Three thousand four hundred ninety-eight (3498) were enrolled at U.S. sites and 4578 at ex-U.S. sites. Four thousand forty-seven (4047) patients were assigned rofecoxib 50 mg daily; 4029 were assigned naproxen 1000 mg daily. Only 29% of patients in each group discontinued prior to study termination. Patient exposure (the at-risk period) ranged from 0.5 to 13 months (mean, 8 months; median, 9 months).

Of the 8076 enrolled patients, 79.7% were women. The majority of the study sample was white (68.2%). The mean patient age (at enrollment) was 58.1 years (range 34 to 89 years). More than 25% of the patients were ≥65 years of age and 5.1% were ≥75 years of age. Oral corticosteroids were used by 56% of patients. Prior history of a clinical upper GI event was reported by 7.8% of patients. Antibodies to H. pylori were present at baseline in 43% of patients (Table 2). The 2 groups were well balanced with respect to all baseline demographics variables.

Table 2

VIGOR Study
Baseline Patient Characteristics by Treatment Group

Baseline Demographics	Rofecoxib (N=4047)		Naproxen (N=4029)		Total (N=8076)	
	n	(%)	n	(%)	n	(%)
Gender						
Female	3223	(79.6)	3215	(79.8)	6438	(79.7)
Male	824	(20.4)	814	(20.2)	1638	(20.3)
Age Group						
<65	3050	(75.4)	2959	(73.4)	6009	(74.4)
≥65	997	(24.6)	1070	(26.6)	2067	(25.6)
Ethnic Group						
White	2761	(68.2)	2750	(68.3)	5511	(68.2)
Black	207	(5.1)	202	(5.0)	409	(5.1)
Asian	101	(2.5)	85	(2.1)	186	(2.3)
Hispanic	501	(12.4)	516	(12.8)	1017	(12.6)
Multi-racial	464	(11.5)	466	(11.6)	930	(11.5)
Other	13	(0.3)	10	(0.2)	23	(0.3)
Prior History of Clinical Upper GI Events						
Yes	314	(7.8)	316	(7.8)	630	(7.8)
No	3733	(92.2)	3713	(92.2)	7446	(92.2)
***Helicobacter Pylori* Serological Status**[†]						
Unknown	63	(1.6)	57	(1.4)	120	(1.5)
Negative	2244	(55.4)	2260	(56.1)	4504	(55.8)
Positive	1740	(43.0)	1712	(42.5)	3452	(42.7)
Treatment for Rheumatoid Arthritis at Study Entry						
Corticosteroids	2260	(55.8)	2263	(56.2)	4523	(56.0)
Methotrexate	2263	(55.9)	2269	(56.3)	4532	(56.1)
Other DMARDs[‡]	1847	(45.6)	1826	(45.3)	3673	(45.5)

[†] Serology was measured by the HM-CAP™ method. Values ≤100 were considered negative.
[‡] DMARDs = Disease Modifying Anti-Rheumatoid Drugs (excluding corticosteroids and methotrexate).

2.4 VIGOR–Results

2.4.1 GI Safety

A total of 191 patients had clinical upper GI events reported by the primary investigators that, as prespecified in the data analysis plan (DAP), were eligible for the primary analyses. These reports were referred to the CRC for adjudication. Of these 191 patients, 177 patients had confirmed events, 13 had unconfirmed events and 1 had an event classified as "not an upper GI event" (Table 3). Of the 177 patients with clinical upper GI events that were adjudicated as confirmed, 53 had events that were adjudicated as confirmed, complicated.

Table 3

VIGOR Study
Summary of Eligibility of Clinical Upper GI Events for Primary Analysis

	Rofecoxib (N=4047)		Naproxen (N=4029)		Total (N=8076)	
	n	(%)	n	(%)	n	(%)
Total Number of Patients With Eligible Clinical Upper GI Events	**58**	**(1.4)**	**133**	**(3.3)**	**191**	**(2.4)**
Confirmed Cases	56	(1.4)	121	(3.0)	177	(2.2)
Unconfirmed Cases	2	(<0.1)	11	(0.3)	13	(0.2)
Not an Upper GI Event	0	(0.0)	1	(<0.1)	1	(<0.1)

A summary of the primary results prespecified in the DAP is in Table 4. Note that rates and relative risk are based on the number of patients who had events and not on the number of individual events. That is, each patient is counted only once in each endpoint even if the patient had more than one event. Clinical upper GI events occurred at a rate of 2.08 events per 100 patient-years in the rofecoxib group and 4.49 events per 100 patient-years in the naproxen group. Thus, the relative risk of developing a confirmed clinical upper GI event was 0.46 in patients taking rofecoxib relative to naproxen, corresponding to a 54% reduction in risk in patients treated with rofecoxib ($p<0.001$). Complicated upper GI events occurred at a rate of 0.59 events per 100 patient-years in the rofecoxib group and 1.37 events per 100 patient-years in the naproxen group. Thus, the relative risk of developing a confirmed, complicated upper GI event was 0.43 in patients taking rofecoxib relative to naproxen, corresponding to a 57% reduction in risk in patients treated with rofecoxib ($p=0.005$). "Any GI bleed" occurred at a rate of 1.15 events per 100 patient-years in the rofecoxib group and 3.04 events per 100 patient-years in the naproxen group. Thus, the relative risk of upper or lower GI bleeds was 0.38 in patients taking rofecoxib relative to naproxen, corresponding to a 62%

reduction in risk in patients treated with rofecoxib ($p<0.001$). The risks of confirmed plus unconfirmed clinical upper GI events and confirmed plus unconfirmed, complicated upper GI events were also significantly reduced in patients treated with rofecoxib relative to naproxen (Table 4). Prespecified per-protocol and sensitivity analyses confirmed the results and verified their robustness (see Section 2.4.1.5).

The beneficial effect of rofecoxib in providing a lower risk for all of the endpoints was constant over the entire time course of the trial (i.e., the p-values for the treatment by time interaction were not significant). Therefore, for all of the endpoints, the relative risk was constant over time, the absolute risk diverged over time, and any apparent change in slope over time as appears in several of the time-to-event plots of cumulative incidence (e.g., Figure 2, Figure 3, and Figure 4) is not statistically significant. The apparent visual variation in slope over time in these plots is most likely due to a decreased precision of estimates at later time points caused by decreasing numbers of patients. Because patients entered the study at different times but terminated at the same time, patients who contribute data to time points beyond 6 months (the minimum duration of planned treatment) reflect cohorts of diminishing size based upon time-of-entry. As the number of patients contributing data decrease, small numbers of events can lead to dramatic effects on the apparent cumulative incidence rate illustrated in the plots.

Table 4

VIGOR Study
Summary of Gastrointestinal Safety Endpoints
(Modified Intention-to-Treat)

Endpoint	Treatment Group	N	Number of Patients With Events	PYR[†]	Rates[‡]	Relative Risk[§]		
						Estimate	95% CI	p-Value
Primary Endpoint								
Confirmed, clinical upper GI events	Rofecoxib	4047	56	2697	2.08	0.46	(0.33, 0.64)[¶]	<0.001
	Naproxen	4029	121	2694	4.49			
Secondary Endpoints								
Confirmed, complicated upper GI events	Rofecoxib	4047	16	2699	0.59	0.43	(0.24, 0.78)	0.005
	Naproxen	4029	37	2698	1.37			
Confirmed and unconfirmed clinical upper GI events	Rofecoxib	4047	58	2697	2.15	0.44	(0.32, 0.60)	<0.001
	Naproxen	4029	132	2693	4.90			
Confirmed and unconfirmed complicated upper GI events	Rofecoxib	4047	17	2699	0.63	0.40	(0.23, 0.71)	0.002
	Naproxen	4029	42	2697	1.56			

Table 4 (Cont.)

VIGOR Study
Summary of Gastrointestinal Safety Endpoints
(Modified Intention-to-Treat)

Endpoint	Treatment Group	N	Number of Patients With Events	PYR[†]	Rates[‡]	Relative Risk[§]		
						Estimate	95% CI	p-Value
Exploratory Endpoint								
Any GI bleed	Rofecoxib	4047	31	2698	1.15	0.38	(0.25, 0.57)	<0.001
	Naproxen	4029	82	2694	3.04			

† Patient-years at risk.
‡ Per 100 PYR.
§ Relative risk of rofecoxib with respect to naproxen from Cox model stratified by prior history of clinical Upper GI events (and study region for confirmed and unconfirmed clinical upper GI events).
¶ 95.44% CI for primary endpoint (i.e., adjustment for the interim analysis).

2.4.1.1 Primary Endpoint

The primary endpoint for VIGOR was a confirmed clinical upper GI event. Fifty-six rofecoxib patients and 121 naproxen patients experienced one or more confirmed clinical upper GI events representing rates of 2.08 and 4.49 per 100 patient-years at risk, respectively. Note that patients are counted only once in each endpoint even if they have more than one event. The relative risk from the Cox model, stratified by prior history of clinical upper GI events, was 0.46 (95.44% CI: 0.33, 0.64; $p<0.001$). The p-value and CIs were adjusted using an α spending function for an interim analysis that had been performed. There was no evidence of interaction between treatment and the stratification variable: prior history of clinical upper GI events ($p=0.874$). Time-to-event plots are shown in Figure 1. A summary of the different types of clinical upper GI events that occurred is in Table 5.

Figure 1

VIGOR Study
Primary Endpoint—Confirmed Clinical Upper GI Events
Time-to-Event Plot
(Modified Intention-to-Treat)

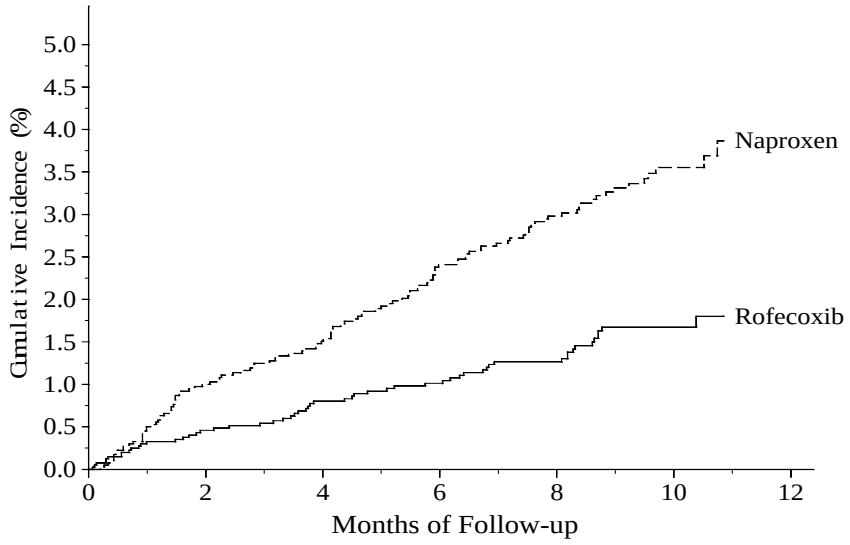


Table 5

VIGOR Study
Number (%) and Type of Confirmed Clinical Upper GI Events
(Primary Endpoints)

Primary Endpoint	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Confirmed Clinical Upper GI Events	**56**	**(1.38)**	**121**	**(3.00)**
Gastroduodenal perforations	3	(0.07)	4	(0.10)
Gastric ulcers	28	(0.69)	81	(2.01)
Duodenal ulcers	27	(0.67)	39	(0.97)
Gastric outlet obstructions	1	(0.02)	0	(0.00)
Upper GI bleeds	14	(0.35)	35	(0.87)
Patients may be counted in more than one row, but are only counted once within a row.				

Although the risk reduction for a confirmed clinical upper GI event for rofecoxib compared with naproxen was constant over time, the curves did not begin to show separation until approximately 1 month of therapy. However, it is important to note that, consistent with clinical treatment of RA, approximately 83% of patients were taking nonselective NSAIDs at the time of screening for this study. In addition, the VIGOR protocol required only a 3-day "washout" of previous NSAIDs prior to patients being randomized to ensure that study therapy did not overlap with previous therapy. Importantly, events occurring as early as the first day of study therapy were included in the modified intention-to-treat analyses. It is likely that some of these early events may have resulted from preexisting asymptomatic ulcers associated with the patient's prior NSAID use and not the assigned study therapy. A sensitivity analysis excluding these and other patients who, according to predefined criteria, might have confounded the primary analysis is described in Section 2.4.1.5 Per-Protocol and Sensitivity Analyses. In these per-protocol and sensitivity analyses, the rofecoxib and naproxen time-to-event curves separated early, lending credence to the supposition that one reason that the time-to-event curves in the primary analysis did not separate at early time points may have been due to confounded events.

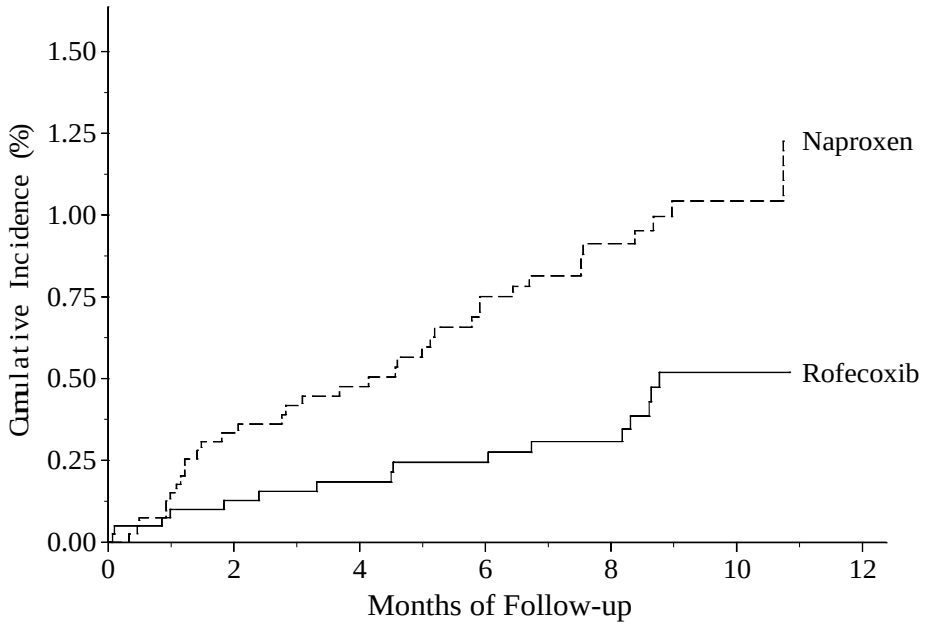
2.4.1.2 Key Secondary Endpoint

The key secondary endpoint for VIGOR was time to first occurrence of a confirmed, complicated upper GI event. Sixteen rofecoxib patients and 37 naproxen patients experienced one or more confirmed, complicated upper GI events with rates of 0.59 and 1.3 per 100 patient-years at risk, respectively. The relative risk from the Cox model

stratified by prior history of clinical upper GI events was 0.43 (95% CI: 0.24, 0.78; p=0.005). There was no evidence of interaction between treatment and prior history of clinical upper GI events (p=0.976). Time-to-event plots are in Figure 2. Of the 53 patients with complicated upper GI events, the majority had major upper GI bleeds (12 patients in the rofecoxib and 32 in the naproxen group.) To explore this endpoint further, a non-prespecified analysis was performed that considered only these confirmed, complicated upper GI bleeds. This analysis demonstrated a 63% reduction in the rofecoxib compared with the naproxen treatment groups (RR = 0.37; 95% CI: 0.19, 0.73).

Figure 2

VIGOR Study
Confirmed, Complicated Upper GI events
Time-to-Event Plot
(Modified Intention-to-Treat)



2.4.1.3 Additional Secondary Endpoints

Additional secondary endpoints were: relative risks for confirmed plus unconfirmed, clinical upper GI events and confirmed plus unconfirmed, complicated upper GI events. Confirmed plus unconfirmed, clinical upper GI events and confirmed plus unconfirmed, complicated upper GI events represent investigator-reported events and provide information that may correspond to the experience in clinical practice where diagnostic

criteria may be less rigid than those applied by the CRC. The overall relative risk for rofecoxib versus naproxen was 0.44 (95% CI: 0.32, 0.60; p<0.001) for confirmed plus unconfirmed clinical upper GI events and 0.40 (95% CI: 0.23, 0.71; p=0.002) for confirmed plus unconfirmed, complicated upper GI events. These relative risk reductions were consistent with and support the reductions seen in the primary and key secondary endpoints (Table 4).

2.4.1.4 Exploratory Endpoint—Any GI Bleed

Determination of the relative risk of bleeding from any location in the GI tract in patients taking 50 mg rofecoxib compared with patients taking 1000 mg naproxen was a prespecified exploratory objective. GI bleeds from any location in the GI tract were defined prior to unblinding as follows:

a. Upper GI bleeds adjudicated by the CRC as confirmed or unconfirmed.

b. Upper GI bleeds adjudicated by the CRC as "not an upper GI event." These were included in this analysis if they met one of the following criteria:

   - Reported as a serious adverse experience;
   - Associated with a 2-g/dL drop in hemoglobin from baseline within 14 days before the start date of the event and or 30 days after.

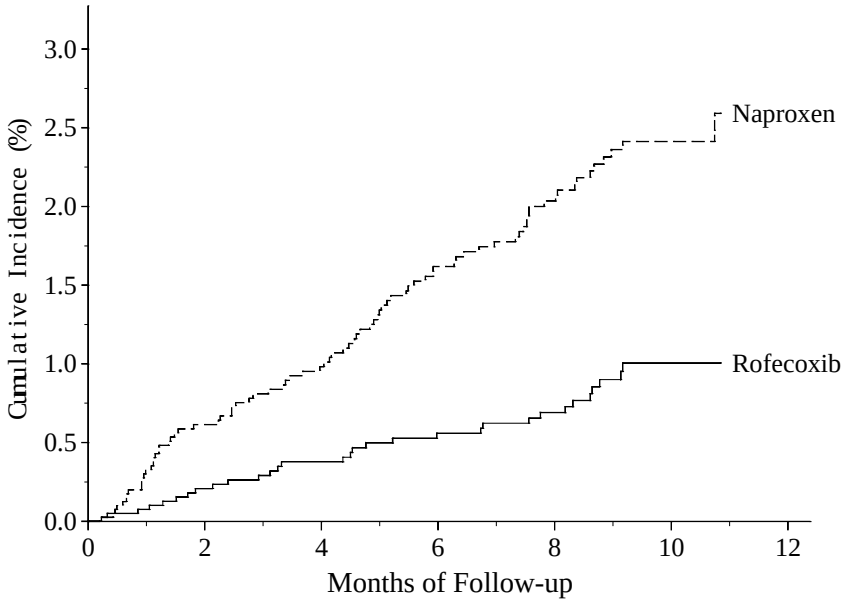
c. Adverse experiences suggestive of a lower GI bleed or GI bleed of unspecified location identified from the adverse experience and serious adverse experience forms. These events were not reviewed by the CRC. The adverse experience terms to be included were identified prior to unblinding. To be included in this analysis, the adverse experiences must have met one of the following criteria:

   - Reported as a serious adverse experience;
   - Resulted in discontinuation of the patient from the study;
   - Associated with a 2-g/dL drop in hemoglobin from baseline within the period extending from 14 days before to 30 days after the start date of the event.

By these definitions, 31 rofecoxib patients and 82 naproxen patients experienced one or more GI bleeds with rates of 1.15 and 3.04, respectively, per 100 patient-years at risk. The relative risk from the Cox model, stratified by prior history of any GI bleed, was 0.38 (95% CI: 0.25, 0.57; p<0.001). There was no evidence of interaction between treatment and prior history of clinical upper GI events (p=0.244). Time-to-event plots are in Figure 3. A non-prespecified analysis of the subgroup of GI bleeds at any site beyond the duodenum (lower GI bleeds) found a 54% reduction in the rofecoxib group compared with the naproxen group (RR = 0.46; 95% CI: 0.22, 0.94).

Figure 3

VIGOR Study
Any GI Bleed
Time-to-Event Plot (Modified Intention-to-Treat)



2.4.1.5 Per-Protocol and Sensitivity Analyses

In addition to the primary modified intention-to-treat analysis, prespecified sensitivity analyses, additional sensitivity analyses, and prespecified per-protocol analyses were conducted. All of these were highly consistent with the results obtained in the primary analysis.

Several sensitivity analyses were prespecified in the DAP to assess the robustness of results to dropouts. Several imputation schemes were applied and the resulting analyses provided generally similar results and supported the overall conclusions. In addition. a prespecified sensitivity analysis excluding clinical upper GI events with possible confounding causes (such as the reported concomitant use of nonstudy NSAID) was performed. This indicated that the relative risk for a confirmed clinical upper GI event was 0.42 (95% CI: 0.30, 0.58) and for a confirmed complicated upper GI event was 0.36 (95% CI: 0.19, 0.68).

Additional sensitivity analyses included all confirmed clinical upper GI events occurring within 45 days of the last dose of study therapy and a second included all confirmed clinical upper GI events through the trial termination in all patients regardless of whether or not they discontinued early. The latter represents the intention-to-treat analysis described in Section 2.1. Both of these analyses demonstrated significant reductions in the incidence of confirmed clinical upper GI events in the rofecoxib group compared with the naproxen group (45 day: relative risk 0.44; 95% CI: 0.32, 0.60; $p<0.001$; End of trial: relative risk 0.47; 95% CI: 0.35, 0.63; $p<0.001$).

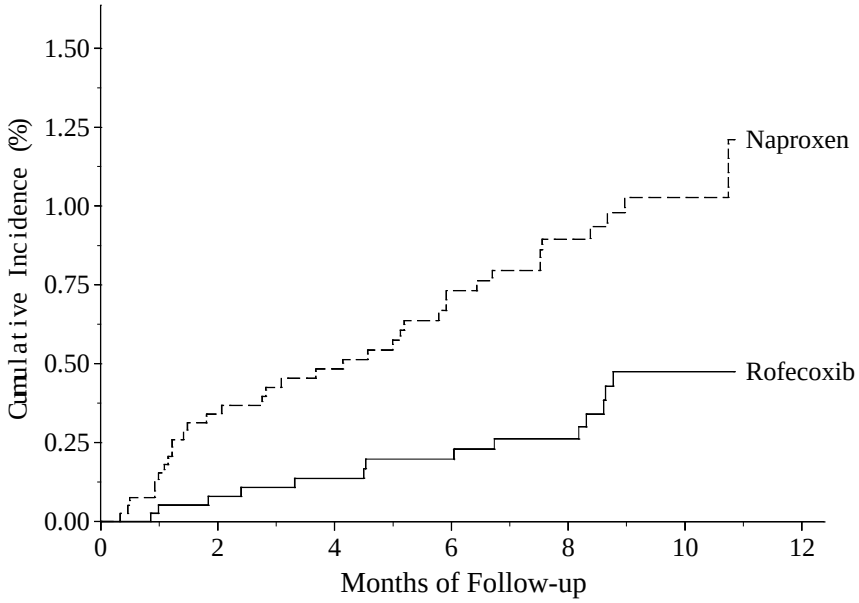
Prespecified, per-protocol analyses were also performed to test the data for robustness. These used a set of prespecified criteria whose intent was to exclude, in a blinded manner, patients who had clinically important protocol deviations that might have confounded the results. For example, because the study only required a minimum of a 3-day washout period for prior NSAID, it is likely that some of the events detected in the first days of the study were a consequence of prior nonselective NSAID use. Therefore, one of the criteria for the per-protocol analyses was the exclusion of patients who had events within the first 2 days of study start who had taken prestudy nonselective NSAIDs, aspirin, or products containing these within 14 days prior to study start.

The per-protocol analyses were consistent with and confirmed the results of the modified intention-to-treat approach. For the primary endpoint, the relative risk for development of a confirmed clinical upper GI event in the per-protocol analysis for rofecoxib versus naproxen was 0.42 (95% CI: 0.30, 0.59; $p<0.001$). For development of a confirmed, complicated upper GI event, the relative risk in the per-protocol analysis was 0.39 (95% CI: 0.21, 0.72; $p=0.003$). Time-to-event plots of development of a confirmed, complicated upper GI event using the per-protocol approach are shown in Figure 4. In contrast to the modified intention-to-treat analysis of confirmed, complicated upper GI events (Figure 2), visual inspection of the curves from the per-protocol analysis reveals an immediate and clear separation between the curves for rofecoxib and naproxen, thus lending credence to the possibility that some early events may have been attributable to a patient's use of prestudy NSAIDs, aspirin, or products containing these within 14 days prior to study start.

The consistency of these additional analyses provide further evidence of the robustness of VIGOR data.

Figure 4

VIGOR Study
Confirmed, Complicated Upper GI events
Time-to-Event Plot (Per Protocol)



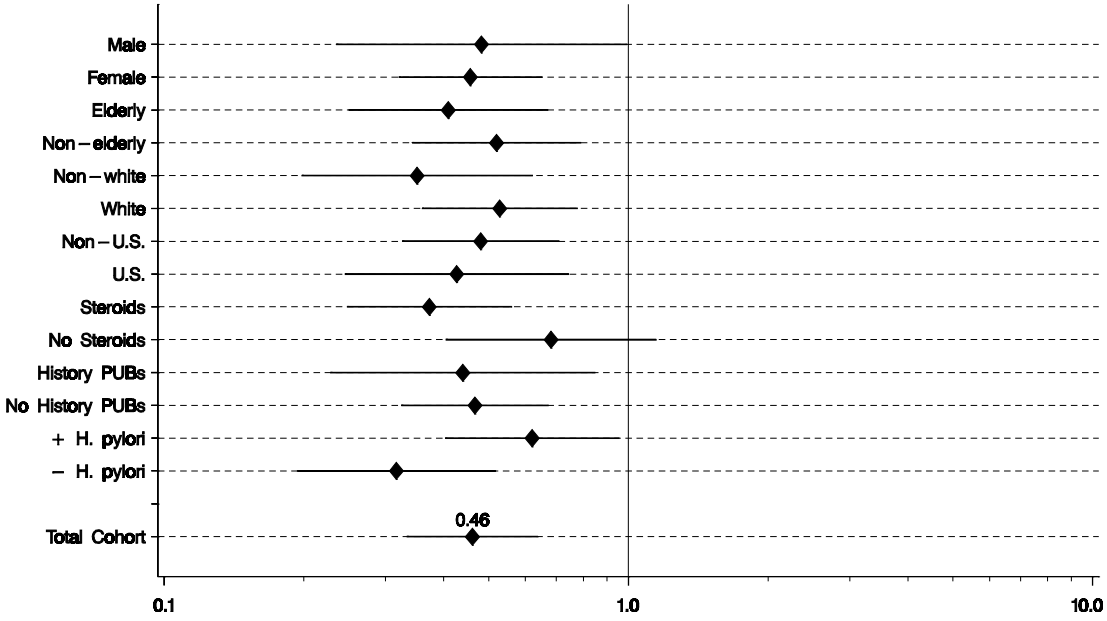
2.4.1.6 Subgroup Analyses

The consistency of treatment effects for rofecoxib and naproxen on the primary endpoint, confirmed clinical upper GI event, was evaluated among various subgroups of patients classified according to demographic parameters (age, gender, race) and the presence of risk factors which predispose patients to the development of a clinical upper GI event (corticosteroid use at baseline, history of a clinical upper GI event, advanced age, and positive serology for *Helicobacter pylori*). These are shown in Figure 5. The study was not powered to detect statistically significant reductions in each of the subgroups, rather, consistency of treatment effects in each subgroup was assessed by performing statistical testing on treatment by subgroup interactions Except for H. pylori, discussed below, these analyses did not demonstrate a statistically significant treatment-by-subgroup interaction ($p>0.05$ for all other treatment by subgroup interactions) implying that the treatment effect was similar in these subgroups. Surprisingly, significant reductions were demonstrated in all subgroups tested except for the subgroup of patients who were not

using corticosteroids at baseline. While there were numerical differences in the magnitude of the reduction in corticosteroid users versus nonusers, as noted above, the treatment by subgroup interaction was not significant which supports the similarity of treatment effect in these subgroups. Of note, the magnitude of reduction in clinical upper GI events in patients with OA (Section 3.5), none of whom were on corticosteroids, was similar to that seen in VIGOR, confirming that corticosteroid users versus nonusers have similar reductions in clinical upper GI events.

Figure 5

VIGOR Study
Relative Risk of Confirmed Clinical Upper GI Events With 95% CI
Within Prespecified Subgroup Cohorts



Serological evidence of H. pylori infection is an independent risk factor for the development of gastroduodenal ulcers. Because H. pylori-negative patients would have a lower background incidence of clinical upper GI events, it had been suggested that these patients might have larger reductions in relative risk of a clinical upper GI event with rofecoxib treatment compared with naproxen treatment than would patients who were positive for H. pylori. Indeed, this was observed in VIGOR. The risk of developing a

confirmed clinical upper GI event in the rofecoxib group was reduced both in patients who were negative and positive for H. pylori but the reduction was greater in patients that were negative for H. pylori. The estimated relative risks were 0.32 (95% CI: 0.19, 0.52) in patients who were negative and 0.62 (95% CI: 0.40, 0.95) in patients who were positive for H. pylori; a significant treatment-by-subgroup interaction was observed for H. pylori seropositivity at baseline (p=0.043). This interaction is not unexpected, since it is known that H. pylori is an independent risk factor, especially for the development of duodenal ulcers. Therefore H. pylori positive patients would be expected to have a background rate of ulcers independent of NSAID use.

2.4.1.7 Discontinuations Due to Digestive System Adverse Experiences

Digestive system adverse experiences are common in patients using NSAIDs and often result in the need to discontinue the medication. A prespecified analysis of discontinuations due to a digestive system adverse experience was performed. A digestive system adverse experience was predefined as any of the terms which map to "Digestive System" in the adverse experience dictionary plus the term abdominal pain (which maps to "Body as a Whole/Site Unspecified" in the dictionary). Three hundred seven (7.6%) patients in the rofecoxib and 416 (10.3%) patients in the naproxen groups discontinued due to a digestive system adverse experience. The rate of discontinuations due to a digestive system adverse experience was significantly lower in patients treated with rofecoxib 50 mg than in patients treated with naproxen 1000 mg (relative risk 0.73; 95% CI: 0.63, 0.85; p<0.001).

An additional analysis of the most common adverse experiences leading to discontinuation was performed to further explore this result. In VIGOR, the most common adverse experiences leading to discontinuation, excluding the clinical upper GI event endpoints, were upper GI symptom adverse experiences (i.e., dyspepsia, abdominal pain, epigastric discomfort, nausea, and heartburn). The total number of patients who discontinued due to any of these 5 upper GI symptom adverse experiences was 142 (3.5%) in the rofecoxib and 196 (4.9%) in the naproxen group (difference = 1.4, 95% CI of difference: 0.5, 2.3). (See Section 4.2.1 for ground rules on the statistical analysis of adverse experiences.) The demonstration that rofecoxib is better tolerated in terms of upper GI symptoms and less likely to result in discontinuation of treatment compared with naproxen is of clinical importance to patients and to the physicians who treat them.

2.4.1.8 Effect of Rofecoxib on Use of Gastroprotective Agents and Upper GI Procedures

In VIGOR, there were no predefined therapeutic algorithms for the diagnosis or treatment of patients with new GI symptoms. Investigators were instructed to care for patients according to their usual practice. For example, GI symptoms in a patient may have prompted the use of a gastroprotective agent (GPA). Such use was captured even if the patient discontinued from the study as a result of prohibited medication use. Other patients may have required a procedure. Thus, VIGOR provided an opportunity to explore further the impact of rofecoxib treatment on medical care utilization. An analysis

was performed of the proportions of patients with new GPA usage (i.e., H_2 antagonists, proton pump inhibitors, sucralfate, and misoprostol) initiated after randomization and investigator-initiated upper GI procedures (upper-GI radiologic studies and upper GI endoscopies). Fewer patients treated with rofecoxib required new GPAs (11.2% versus 14.5% of patients, $p<0.001$) and had upper GI procedures (5.6% versus 6.9% of patients, $p=0.02$) compared with patients treated with naproxen. Similar results were seen in an analysis restricted to the subset of patients reporting GI adverse experiences.

2.4.2 Efficacy for the Treatment of RA in VIGOR

VIGOR was not designed to rigorously establish the efficacy of rofecoxib in the treatment of RA. The efficacy of rofecoxib in the treatment of RA will be established by 2 Phase III studies designed to test the efficacy hypotheses. VIGOR differs from those studies in the following ways: patients were not required to meet RA flare criteria; changes in disease-modifying antirheumatic drug (DMARD) therapy were allowed without restriction throughout VIGOR; and its scope and complexity did not make this trial well suited for the assessment of efficacy. Nonetheless, it was important to establish that the safety comparisons in VIGOR involved doses of the drugs that provided similar clinical efficacy.

The efficacy parameters in this study included standard measures of efficacy in RA trials: Patient's and Investigator's Global Assessment of Disease Activity, measured on the Likert scale from 0 (Very Well) to 4 (Very Poor); the modified Health Assessment Questionnaire (HAQ), a disease-specific quality of life questionnaire consisting of 8 questions measured on a scale of 0 (Without any Difficulty) to 3 (Unable to Do); and discontinuations due to lack of efficacy. The modified HAQ, which was measured only at sites in the U.S. (because of a lack of validated translations in all countries outside the U.S.), was predefined as an exploratory endpoint. Because this study did not employ a disease "flare" design, the treatment effect was expected to remain constant over the treatment period and not demonstrate large improvements from baseline. Patient's and Investigator's Global Assessment of Disease Status and modified HAQ were summarized as the average change from baseline over the treatment period; this represented an integrated measure of the overall level of efficacy experienced during the study. In addition, the rate of patient discontinuation for lack of efficacy was used to further explore possible differences in efficacy between treatment groups.

Although the study had substantial power to detect very small, significant differences between the groups, there were no observed differences between treatments in their effects on patient and investigator global assessments of disease status and the modified HAQ. For all 3 endpoints, the least-squares (LS) means of the difference between the 2 treatment groups ranged from –0.00 to 0.01 with 95% confidence intervals that all included 0 (Table 6).

Table 6

VIGOR Study
Efficacy Measures—Average Over Treatment Period (Modified Intention-to-Treat)

Treatment Group	N	Baseline		On-Treatment		Change From Baseline			
		Mean	SD	Mean	SD	Mean[†]	SD	LS Mean[‡]	95% CI[‡]
Patient's Global Assessment of Disease Activity (0 to 4 Likert)									
Rofecoxib	3835	1.96	0.93	1.45	0.79	-0.51	0.93	-0.51	(-0.54, -0.47)
Naproxen	3838	1.99	0.94	1.46	0.80	-0.53	0.94	-0.51	(-0.54, -0.47)
R-N[§]						0.02	0.93	-0.00	(-0.03, 0.03)
Investigator's Global Assessment of Disease Activity (0 to 4 Likert)									
Rofecoxib	3832	1.85	0.80	1.36	0.69	-0.49	0.84	-0.48	(-0.51, -0.45)
Naproxen	3839	1.87	0.78	1.36	0.69	-0.52	0.85	-0.49	(-0.52, -0.46)
R-N[§]						0.03	0.84	0.01	(-0.02, 0.04)
Modified HAQ (U.S. Sites Only) (0 to 3 Likert)									
Rofecoxib	1603	0.59	0.49	0.49	0.46	-0.11	0.37	-0.10	(-0.12, -0.07)
Naproxen	1621	0.59	0.49	0.47	0.44	-0.12	0.36	-0.11	(-0.13, -0.09)
R-N[§]						0.01	0.37	0.01	(-0.01, 0.04)

[†] Negative numbers mean improvement.
[‡] Least-square means and 95% CI are from ANOVA model with treatment, prior history of clinical upper GI events, study region (U.S./multinational), and baseline value as a covariate. Modified HAQ was only administered in the U.S., therefore the model for this parameter does not include study region.
[§] Negative numbers for mean and LS mean favor rofecoxib, positive numbers favor naproxen.

A prespecified analysis of discontinuations due to lack of efficacy demonstrated that such discontinuations were infrequent in both treatment groups and there was no difference between the treatment groups (Table 7). Discontinuation rates were 9.6 per 100 patient-years for rofecoxib and 9.9 per 100 patient-years for naproxen, with a relative risk for rofecoxib with respect to naproxen of 0.97 (95% CI 0.82, 1.16; p=0.769).

Table 7

VIGOR Study
Prespecified Analysis of Withdrawal From Study Due to Lack of Efficacy

Withdrawal Due to:	Treatment Group	N	Number of Patients	PYR[†]	Rates[‡]	Relative Risk[§]		
						Estimate	95% CI	p-Value
Lack of efficacy	Rofecoxib	4047	256	2654	9.6	0.97	(0.82, 1.16)	0.769
	Naproxen	4029	263	2655	9.9			

[†] Patient-years at risk.
[‡] Per 100 PYR.
[§] Relative risk of rofecoxib with respect to naproxen from Cox Model stratified by prior history of clinical upper GI events and study region (U.S./Non-U.S.).

Data from Phase IIb studies with rofecoxib in RA suggest that rofecoxib 25 mg once daily provided maximal efficacy in the treatment of RA [40]. Additionally, recently completed Phase III studies in RA not yet reviewed by the FDA suggest that rofecoxib 12.5 mg is partially effective, while rofecoxib 25 mg is a fully efficacious dose and similar to rofecoxib 50 mg and naproxen 1000 mg in the treatment of RA. Therefore, it is anticipated that 25 mg will be the recommended dose of rofecoxib for RA.

The efficacy results of the VIGOR trial provide confirmation that rofecoxib 50 mg and naproxen 1000 mg provide at least similar efficacy, thus validating these doses for the GI safety comparisons.

2.5 VIGOR–GI Safety Conclusions

- In RA patients, rofecoxib 50 mg daily (2 to 4 times the recommended dose in OA and 2 times the anticipated dose in RA) is associated with significantly fewer clinical upper GI events, complicated upper GI events, and any GI bleeding than 1000 mg daily of the nonselective NSAID naproxen. The risk reduction with rofecoxib in VIGOR ranged from 54% for confirmed clinical upper GI events and 57% for confirmed, complicated upper GI events to 62% for any GI bleed.

- Rofecoxib demonstrates consistency of effect in reducing the risk of clinical upper GI events in the subgroups of patients defined by age, gender, race, corticosteroid use, and history of a clinical upper GI event, implying similar risk reduction in these subgroups. In addition, rofecoxib reduces the risks of clinical upper GI events in patients with and without serologic evidence of H. pylori infection.
- Rofecoxib 50 mg and naproxen 1000 mg provided similar efficacy in the treatment of RA, thus safety comparisons between these doses is clinically meaningful.

3. Review of the Rofecoxib Gastrointestinal Safety Program Prior to VIGOR

The reduced risk of clinical upper GI events, complicated upper GI events, and GI bleeds in RA patients taking rofecoxib as compared to naproxen in VIGOR confirms the results of previous studies. These previous studies, submitted in the Original NDA and evaluated by the FDA and this Committee in Apr-1999, consisted of intestinal permeability and GI blood loss studies in healthy subjects, a proof-of-concept endoscopy study in healthy subjects, 2 Phase III, 6-month endoscopic surveillance studies in OA patients, and a predefined combined analysis of clinical upper GI events in all 8 Phase IIb/III OA clinical trials. Rofecoxib was compared to the nonselective NSAIDs aspirin, indomethacin, diclofenac, ibuprofen, and nabumetone in these studies. As reviewed in this section, the studies and combined analysis demonstrate that rofecoxib use is associated with significantly less GI mucosal damage than nonselective NSAIDs and, in OA patients, fewer endoscopically detected ulcers and fewer clinical upper GI events. Indeed, the magnitude of the GI safety benefit demonstrated in OA patients (55% reduction in clinical upper GI events) is numerically similar to that observed in RA patients in VIGOR (54% reduction). Together, the results conclusively demonstrate that NSAID gastropathy is associated with the inhibition of COX-1 by nonselective NSAIDs and that the use of the highly selective COX-2 inhibitor rofecoxib greatly reduces the risk of NSAID-type GI damage.

3.1 Intestinal Permeability and GI Blood Loss Studies

Chronic use of nonselective NSAIDs can increase intestinal permeability as a marker of breaks in GI mucosal integrity [41; 42]. Intestinal permeability and GI blood loss studies showed that damage in the GI tract associated with rofecoxib was comparable to placebo and less than that seen with the comparator nonselective NSAIDs indomethacin and ibuprofen.

Rofecoxib 25 mg and 50 mg once daily were compared with indomethacin 50 mg 3 times daily and placebo in a Phase II crossover study of intestinal permeability. Permeability was measured by comparing urine levels of orally administered ^{51}Cr-EDTA (a substance not normally absorbed) to levels of orally administered L-rhamnose (a substance freely absorbed). After 7 days, rofecoxib 25 mg and 50 mg each produced significantly less change in intestinal permeability than indomethacin and satisfied the prespecified criteria for comparability to placebo. In contrast, indomethacin produced a significant increase in intestinal permeability versus placebo.

Another marker for GI tract toxicity, drug-induced bleeding, was assessed by studying the fecal loss of ^{51}Cr-labeled erythrocytes [43]. In a Phase II parallel-group study, healthy subjects received either rofecoxib 25 mg or 50 mg once daily, ibuprofen 800 mg 3 times daily, or placebo for 4 weeks. A portion of each subject's erythrocytes were labeled with ^{51}Cr and then reinfused back to the subject. The average daily ^{51}Cr red blood cell loss in stool was computed. Rofecoxib 25 mg and 50 mg daily each met prespecified criteria for comparability to placebo. Rofecoxib 25 mg and 50 mg daily were each associated with significantly less blood loss than ibuprofen. Ibuprofen produced significantly greater fecal blood loss compared with placebo.

3.2 Proof-of-Concept Endoscopy Study and Phase III Endoscopic Surveillance Studies

Proof-of-Concept Endoscopy Study in Healthy Subjects

In the spectrum of NSAID gastropathy, erosions are the earliest disruption in GI mucosal integrity that can be visualized by endoscopy [44; 45]. Analysis of erosions after administration of high-dose rofecoxib was part of the "proof-of-concept" Phase I program. One hundred-seventy (170) healthy subjects were administered rofecoxib 250 mg daily (10 times the maximum approved dose for chronic use), ibuprofen 800 mg 3 times daily, aspirin 650 mg 4 times daily, or placebo for 7 days in a parallel-group, double-blind, randomized study. The percent of subjects with erosions was 8.0 for placebo (N=50), 12.2 for rofecoxib (N=49), 70.6 for ibuprofen (N=51) and 94.1% for aspirin (N=17). Aspirin and ibuprofen were each associated with significantly more erosions than rofecoxib or placebo ($p<0.001$ for rofecoxib versus aspirin, rofecoxib versus ibuprofen, placebo versus aspirin, and placebo versus ibuprofen); rofecoxib and placebo were not significantly different from each other.

Phase III Endoscopy Studies in OA Patients

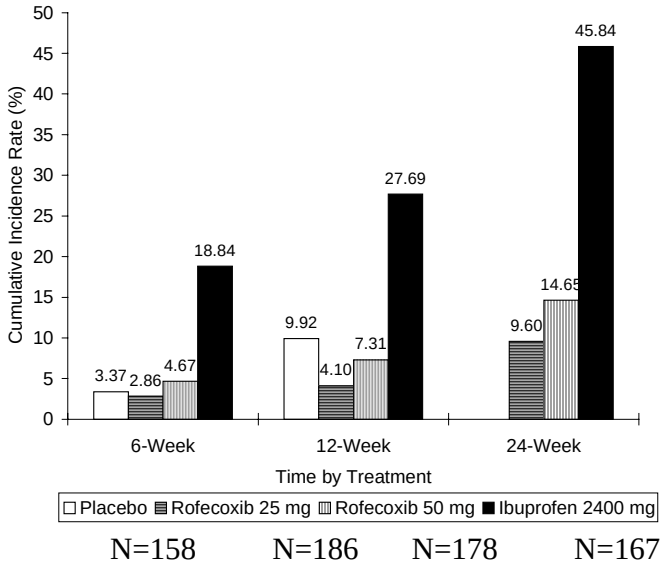
The majority of complicated upper GI events associated with NSAIDs have, as their proximate cause, a gastric or duodenal ulcer [8]. Two replicative 6-month upper endoscopy studies, identical in design, were performed in OA patients. Approximately 750 patients (mean age, 62 years) were enrolled in each of the 2 studies. Patients were randomized to receive either rofecoxib 25 mg daily, rofecoxib 50 mg daily, ibuprofen 800 mg 3 times daily, or placebo. The 25- and 50-mg doses of rofecoxib are 1 to 2 and 2 to 4 times the recommended dose for the treatment of OA, respectively. Patients underwent endoscopy at baseline, and at 6, 12, and 24 weeks of treatment. For both ethical and practical reasons, there was a desire to limit placebo treatment of patients with OA. Therefore, 95% of placebo-treated patients underwent scheduled discontinuation at Week 16 and, to maintain blinding, 5% of the patients in the other groups were randomly discontinued at the same time. These Phase III 24-week endoscopy studies in OA patients showed that rofecoxib 25 mg and 50 mg daily had significantly lower incidence rates for gastroduodenal ulcers ≥3 mm and ≥5 mm at 12 and 24 weeks compared with ibuprofen. The results for ulcers ≥3 mm (the primary endpoint) are in Figure 6. Similar results were obtained in the analysis of ulcers ≥5 mm. A subgroup analysis showed that the risk of developing a gastroduodenal ulcer was increased in patients ≥65 years, in patients with a history of a clinical upper GI event, and in patients with erosions at baseline. The superior GI safety of rofecoxib over ibuprofen was maintained in each of these subgroups.

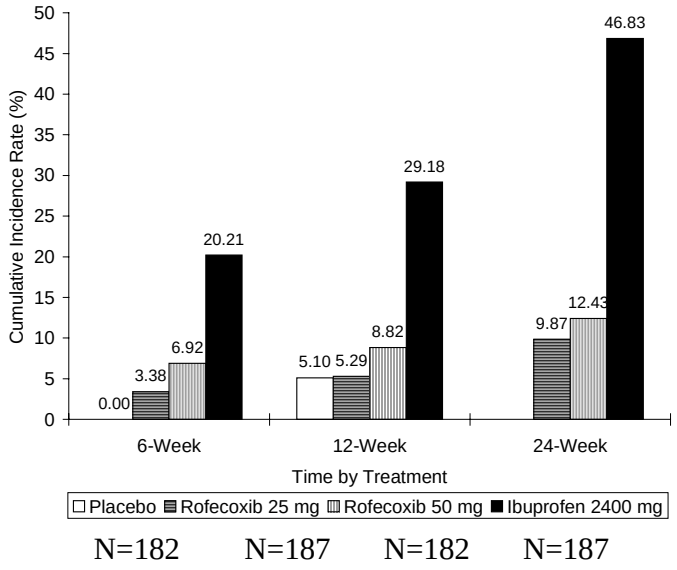
Published animal studies suggest that COX-2 might be important in ulcer healing [46 to 48]. To investigate the clinical relevance of these findings, the Phase III endoscopy studies included patients with baseline erosions. If COX-2 were important in gastroduodenal mucosal healing in patients, then individuals with baseline erosions

would have been expected to develop more overt ulcers on rofecoxib than placebo. A pooled analysis of Protocols 044 and 045 showed that a total of 202 patients in these studies had one or more erosion at baseline endoscopy; 48 in the placebo group, 51 in the rofecoxib 25-mg groups, 45 in the rofecoxib 50-mg group, and 58 in the ibuprofen group. In this subgroup of patients, the cumulative number of ulcers detected at 12 weeks was 7 for the placebo group, 8 for the rofecoxib 25-mg group, 8 for the rofecoxib 50-mg group and 22 for the ibuprofen group. Thus, the ulcer rate in patients with baseline erosions was similar in the rofecoxib 25-mg, rofecoxib 50-mg, and placebo groups. These data favor the interpretation that inhibition of COX-2 does not interfere with gastroduodenal mucosal healing.

Figure 6

Replicative Phase III Endoscopy Studies P044 and P045 in OA Patients
Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥3 mm
(Intention-to-Treat)





For both Protocols 044 and 045, $p<0.001$ for ibuprofen versus placebo, rofecoxib 25 mg, and rofecoxib 50 mg at Week 12 and for rofecoxib 25 mg and rofecoxib 50 mg at Week 24. Placebo was not included at Week 24 since 95% of the patients in the placebo group were discontinued at Week 16.

3.3 Prespecified Combined Analysis of Clinical Upper GI Events in the Phase IIb/III OA Program

The Phase II GI safety studies in healthy subjects and the Phase III endoscopic surveillance studies in OA patients provided strong evidence in support of the COX-2 GI safety hypothesis and demonstrated that treatment with rofecoxib resulted in significantly less GI mucosal injury as compared with nonselective NSAIDs. To support the endoscopic findings with a more relevant clinical endpoint, a prespecified combined analysis of all Phase IIb/III OA clinical trials (8 studies including the endoscopy studies) was performed to determine the reduction in risk of developing a clinical upper GI event in patients taking rofecoxib as compared with nonselective NSAIDs. In this analysis, results from all 8 Phase IIb/III OA studies were combined in order to provide enough clinical upper GI events for statistically meaningful comparisons between rofecoxib and nonselective NSAID groups. These 8 studies were similar in several respects. They were all randomized parallel-group studies, with similar adverse experience monitoring procedures. All studies enrolled OA patients. There were similar demographic characteristics across studies (except age in Protocol 058, a study that focused on patients ≥80 years of age). The studies differed with respect to duration of treatment (two 6-month studies, two 1-year studies, and 4 other studies with up to 86 weeks of treatment), inclusion of endoscopic surveillance to detect ulcers, allowance of concomitant aspirin use (in Protocol 058 only), and treatment groups (i.e., different comparator agents and inclusion of placebo in some studies). To address differences in duration, time to the first event for each patient was ascertained by survival analysis. In addition, because many of the ulcers detected at the mandated endoscopies were asymptomatic and, in theory, might have healed without clinical consequence, a prespecified procedure was used to censor ulcers detected within a ±7-day window around mandated endoscopies in the endoscopic surveillance studies.

Cases of all suspected clinical upper GI events were submitted to an independent, blinded case review committee (CRC) for adjudication. The CRC for this analysis had the same structure and used the similar procedures as the CRC for VIGOR. Based on predefined criteria, cases were judged as “confirmed” or “unconfirmed” and as “complicated” or “uncomplicated” (Appendix 1).

The primary comparisons were between the combined group of rofecoxib doses and the combined group of nonselective NSAIDs (nabumetone, ibuprofen, and diclofenac; the comparators used in the OA program). The log-rank test was used to compare cumulative incidence curves among treatment groups. The Cox proportional hazards model was used to estimate the overall relative risk (RR) for developing a clinical upper GI event on rofecoxib versus nonselective NSAIDs. This yielded an estimate of the magnitude of the rofecoxib effect and complemented the log-rank test. Differences in rates and their corresponding confidence intervals (CIs) were calculated using the method of Breslow-Crowley.

The analysis included 3357 patients taking rofecoxib 12.5, 25, or 50 mg (average dose, 24.7 mg), 1564 patients taking nonselective-NSAID comparators (nabumetone 1500 mg, ibuprofen 2400 mg, or diclofenac 150 mg/day) for up to 24 months, and 514 patients on placebo for up to 4 months. In each study, information on clinical upper GI events was collected up to 24 months or for the duration of the study, whichever occurred first. However, the focus was on data from the first 12 months because only 13% of the total population had more than 12 months exposure and no clinical upper GI events were observed after 12 months. Total patient exposure was 1533 patient-years for the rofecoxib group, 647 patient-years in the nonselective-NSAID group, and 112 patient-years in the placebo group.

A total of 49 patients had confirmed clinical upper GI events. As shown in Table 8 and Figure 7, the cumulative incidence of confirmed clinical upper GI events in the rofecoxib group was significantly lower than in the nonselective-NSAID group. The cumulative incidences of confirmed clinical upper GI events over the first 12 months were 1.50 and 2.68 for rofecoxib and nonselective NSAIDs, respectively, yielding a relative risk of 0.45 (95% CI: 0.25, 0.81; p=0.006) for rofecoxib relative to nonselective NSAIDs. To test for robustness, 11 patients were excluded who were found to have asymptomatic ulcers at mandated endoscopies performed, for scheduling reasons, outside the ±7-day window. Even excluding these patients, the rates per 100 patient-years were 1.33 and 2.60 for rofecoxib and NSAIDs, respectively, yielding a relative risk of 0.51 (p=0.046) for rofecoxib relative to NSAIDs. The number of confirmed, complicated upper GI events in this analysis was small (N=14), precluding statistical conclusions. Numerically, the relative risk of confirmed, complicated upper GI events for rofecoxib compared with nonselective NSAIDs (RR=0.51) was similar to the relative risk for confirmed clinical upper GI events (RR=0.45).

Table 8

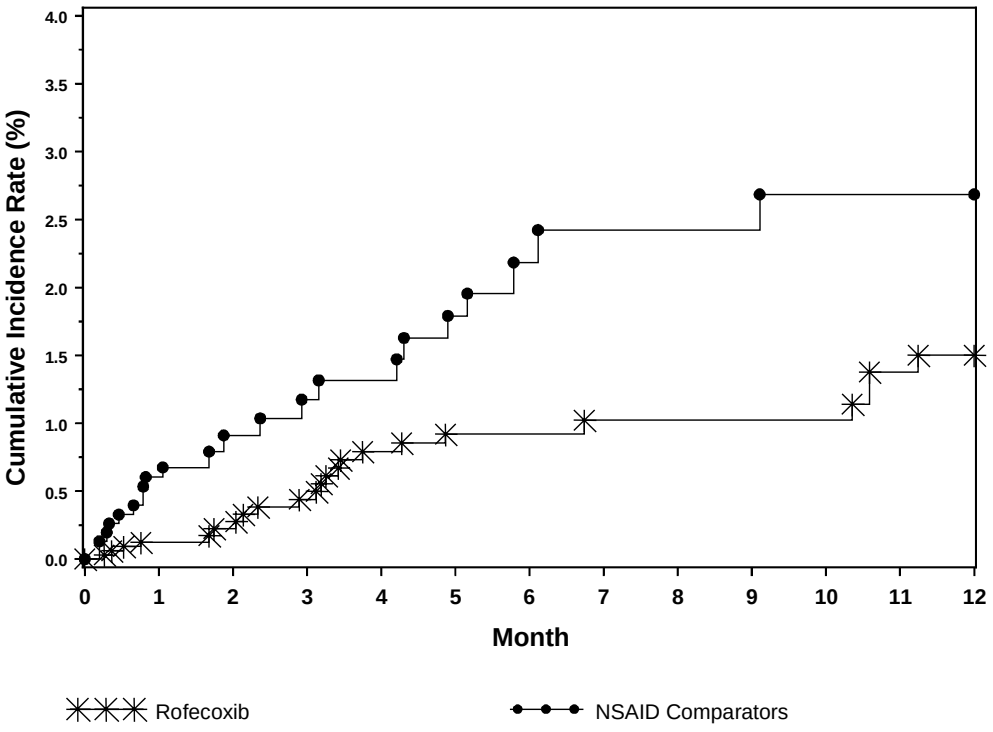
Prespecified Combined Analysis of Clinical Upper GI Events in the Phase IIb/III OA Program
Summary of Survival Analyses for Incidence of Clinical Upper GI Events
(Intention-to-Treat)

Endpoint	Cumulative Incidence[†] (%)			Cumulative Incidence Difference (%)	Relative Risk[‖]	95% CI for Relative Risk	p-Value[¶] for Primary Analysis
	Placebo	Rofecoxib	NSAIDs				
Primary Endpoint							
Confirmed Clinical Upper GI Events							
Rofecoxib versus NSAIDs over 12 months	n/a[§]	1.50	2.68	-1.18	0.45	(0.25, 0.81)	0.006
Secondary Endpoints							
Confirmed + Unconfirmed Clinical Upper GI Events							
Rofecoxib versus NSAIDs over 12 months	n/a[§]	1.50	3.39	-1.89	0.35	(0.20, 0.61)	<0.001
NSAIDs versus placebo over 4 months[‡]	1.23	1.59	4.16	2.93	3.95	(1.32, 11.82)	0.008

[†] Cumulative incidence from the survival analysis; may not equal (number of patients with events/N) x 100.
[‡] Comparisons to placebo were confined to studies containing placebo.
[§] Placebo treatment did not exceed 4 months.
[‖] From the Cox Proportional Hazards Model, rofecoxib relative to NSAIDs or NSAIDs relative to placebo.
[¶] From the log rank test for the comparison of the cumulative incidence curves.

Figure 7

Prespecified Combined Analysis of Clinical Upper GI Events in the Phase IIb/III OA Program
Cumulative Incidence of Confirmed Clinical Upper GI Events



3.4 Conclusions—GI Safety

- Alterations in intestinal permeability with rofecoxib are comparable to placebo, whereas indomethacin increases intestinal permeability
- Fecal red blood cell loss with rofecoxib is comparable to placebo, whereas ibuprofen increases fecal red blood cell loss
- Endoscopic gastroduodenal erosion with rofecoxib is similar to placebo, whereas ibuprofen and aspirin increase the incidence of endoscopic gastroduodenal erosion.
- The incidence of endoscopic gastroduodenal ulcer with rofecoxib is significantly less than with ibuprofen.
- The risk of clinical upper GI events with rofecoxib is reduced approximately 55% relative to nonselective NSAIDs in patients with OA.

3.5 Comparison of VIGOR With the Predefined Combined Analysis of OA Phase IIb/III Clinical Studies

Shown in Table 9 is a comparison of the event rate and risk reduction of clinical upper GI events and complicated upper GI events obtained in VIGOR with those obtained in the combined analysis of clinical GI outcomes in the Phase IIb/III OA program. The table shows both rates of different events calculated per 100 patient-years and the percent decreased risk of events associated with the use of rofecoxib as compared with nonselective NSAIDs. There is overall agreement between these 2 studies despite their different study designs (prospective, single outcomes study versus prospective combined analysis), different patient populations (RA in VIGOR versus OA in the combined analysis), different doses of rofecoxib (50 mg in VIGOR versus an average of 24.7 mg in the combined analysis), and different comparator NSAIDs (naproxen in VIGOR versus ibuprofen/diclofenac/nabumetone in the combined analysis). Although the overall reduction in risk is similar between these 2 studies, the actual rates appear higher in RA patients than in OA patients, consistent with published literature [16]. Nonetheless, the similarity in risk reduction in these 2 populations and the reproducibility of these results across 2 independent data sets and analyses indicate that the GI results from VIGOR may be generalized. These data strongly support the conclusion that the risk of clinically significant GI events in patients taking rofecoxib is meaningfully lower as well as statistically significantly lower than in NSAIDs users.

Table 9

Comparison of Rofecoxib GI Outcomes Studies
Combined Analysis of OA Phase IIb/III Studies Versus VIGOR

	Treatment Group	Phase IIb/III (OA Patients)†	Risk Reduction‡	VIGOR (RA Patients)†	Risk Reduction‡
Confirmed Clinical Upper GI Event	Rofecoxib	1.61	(55%)	2.08	(54%)
	Nonselective NSAIDs	3.58		4.49	
Confirmed and Unconfirmed Clinical Upper GI Events	Rofecoxib	1.61	(65%)	2.15	(56%)
	Nonselective NSAIDs	4.56		4.90	
Confirmed Complicated Upper GI events	Rofecoxib	0.42	(49%)	0.59	(57%)
	Nonselective NSAIDs	0.81		1.37	
Confirmed and Unconfirmed Complicated Upper GI Events	Rofecoxib	0.42	(63%)	0.63	(60%)
	Nonselective NSAIDs	1.14		1.56	

† Event rate (percent per year).
‡ Percent reduction in relative risk.

3.6 Postmarketing Clinical Upper GI Adverse Event Experience With Rofecoxib

To give additional perspective to the occurrence of upper GI events in the clinical setting, reports of clinical upper GI events occurring with rofecoxib as a marketed product were reviewed. The review focused on the marketed experience with rofecoxib only in the United States because: (1) the majority of all marketing experience for calendar year 1999 with VIOXX™ occurred in the United States; (2) limiting the review to a single country minimizes the effects of clinical practice variations on the data; and (3) audited data were available for prescription and sample distribution in the United States. Audited IMS Health Inc. prescription data and data on samples of rofecoxib distributed to health care practitioners were used to determine that there were an estimated 420,170 patient-years of marketed rofecoxib use in the United States for 1999.

From the period 23-May-1999 to 31-Dec-1999, there were 132 reports of potential clinical upper GI events in the United States. Of these, 59 were complicated upper GI events based on the criteria in VIGOR. Most (72.9%) of the patients who developed a

complicated upper GI event during marketed use of rofecoxib had risk factors for such an event. The most common risk factors were aspirin use (32.2%), coumadin use (15.3%), and prior history of ulcer disease (15.3%).

Based on an estimated 420,170 patient-years of marketed rofecoxib use in the United States for 1999, the incidence for reported events ranged from 0.014 per 100 patient-years for reported complicated upper GI event to 0.024 per 100 patient-years for reported clinical upper GI event. These incidences are lower than the incidence of confirmed, complicated upper GI events in the rofecoxib group of VIGOR (0.59 per 100 patient-years) and much lower than the reported incidence of GI hospitalizations due to complications of NSAID gastropathy (1.46 per 100 patient-years) [39]. In patients not exposed to NSAIDs, the hospitalization rate for clinical upper GI events as reported in population-based cohort studies ranges from 0.10 to 0.68 per 100 patient-years [49]. This difference in rates is likely due to incomplete reporting of serious digestive system adverse experiences for rofecoxib as a marketed product. The degree of incomplete reporting is difficult to ascertain. One estimate is that 10 to 15% of serious adverse experiences are reported for marketed products [50]. Even assuming that only 1 in 10 complicated upper GI events during rofecoxib use were reported either to Merck Research Laboratories or to a regulatory agency, the reported incidence of these events is low and consistent with the expected background rate of these events in patients not exposed to NSAIDs [39].

3.7 Discussion of the GI Safety of Rofecoxib

In the VIGOR trial of more than 8000 patients with RA, rofecoxib at twice the maximum dose approved for chronic use demonstrated an improved GI safety profile compared with naproxen in all GI safety endpoints. The risk of developing a confirmed clinical upper GI event was significantly lower in the group treated with rofecoxib than in the group treated with naproxen (RR = 0.46; 95% CI 0.33, 0.64; $p<0.001$), satisfying the primary hypothesis of the study. This corresponds to a risk reduction of 54%. The risk of developing a more severe confirmed, complicated upper GI event was also significantly lower in the group treated with rofecoxib than in the group treated with naproxen (RR = 0.43; 95% CI 0.24, 0.78; $p=0.005$). This corresponds to a risk reduction of 57%. The risk of developing any GI bleed was significantly lower in the group treated with rofecoxib than in the group treated with naproxen (RR = 0.38; 95% CI 0.25, 0.57; $p<0.001$). This corresponds to a risk reduction of 62%.

The results of VIGOR confirmed the results of the combined analysis of clinical upper GI events in all Phase IIb/III studies of patients with OA. In the combined analysis of all Phase IIb/III OA studies, the reduction in confirmed clinical upper GI events in the rofecoxib group compared with the combined NSAID group was 55%. This nearly identical reduction in the risk of confirmed clinical upper GI events in OA and RA patients treated with rofecoxib, and the similar reduction in confirmed, complicated upper GI events seen in both patient populations with rofecoxib, argues strongly for the validity and generalizability of the findings to all patient populations requiring chronic therapy with NSAIDs.

Investigator-reported clinical upper GI events (i.e., confirmed plus unconfirmed clinical upper GI events) provide information pertinent to clinical practice, where rigorous, prespecified diagnostic criteria are not always applied. The risk of developing a confirmed or unconfirmed clinical upper GI event in both the combined analysis of OA studies and in VIGOR was also significantly lower in patients taking rofecoxib as compared with nonselective NSAIDs. In VIGOR, the incidence of both confirmed plus unconfirmed clinical upper GI events and confirmed plus unconfirmed, complicated upper GI events was significantly lower in the group treated with rofecoxib compared with the group on naproxen. The overall relative risk for rofecoxib versus naproxen was 0.44 (95% CI 0.32, 0.60; p<000.1) for confirmed plus unconfirmed clinical upper GI events and 0.40 (95% CI 0.23, 0.71; p=0.002) for confirmed plus unconfirmed, complicated upper GI events. In the combined analysis of all Phase IIb/III OA studies, the overall relative risk of confirmed plus unconfirmed clinical upper GI events for rofecoxib versus nonselective NSAIDs was 0.35 (95% CI 0.20, 0.61; p<0.001).

The reductions in confirmed clinical upper GI events demonstrated in VIGOR and in the combined analysis of OA studies are consistent with the endoscopic studies which showed that rofecoxib 25 mg and 50 mg daily are associated with significantly fewer gastroduodenal ulcers than the nonselective NSAID, ibuprofen. In the endoscopy studies, the relative risk reduction in ulcers with rofecoxib 50 mg daily as compared with ibuprofen 800 mg 3 times daily at 6 months was 71%. Based on the analyses in Figure 1 and Figure 2, the relative risk reduction at 6 months in VIGOR was similar: 58% for confirmed clinical upper GI events and 67% for confirmed, complicated upper GI events. The greater apparent reduction in ulcers in the endoscopy studies may be partly due to the exclusion in these studies of patients with ulcers at baseline contrasted by no such exclusion and a short washout period from prestudy NSAIDs in VIGOR. Approximately 20% of patients screened for entry into the endoscopy studies were excluded due to the presence of baseline ulcers. The observation that these were found after a 2-week washout period suggests further that some of the clinical upper GI events in VIGOR that occurred in the first days after randomization may have reflected preexisting NSAID gastropathy.

VIGOR also included an analysis of all GI bleeds. The risk of developing a GI bleed anywhere in the digestive tract in VIGOR was significantly lower in the group treated with rofecoxib than in the group treated with naproxen (RR=0.38; 95% CI 0.25, 0.57; p<0.001). This corresponds to a risk reduction of 62%. The risk of bleeding from sites in the upper GI tract was reduced by 64% and the risk from sites beyond the duodenum was reduced by 54% with rofecoxib compared with naproxen. The results of this analysis of all GI bleeds confirm the clinical relevance of the special red blood cell loss studies described in the original NDA and in the GI Blood Loss studies (Section 3.1 Intestinal Permeability and GI Blood Loss Studies). Although nonselective NSAIDs are typically associated with upper GI toxicity, an increased incidence of lower GI bleeding has also been reported with use of these agents [51; 52]. The reduced incidence of lower

GI bleeds in patients on rofecoxib compared with naproxen implies that the increase in lower GI bleeds associated with nonselective NSAIDs is also likely mediated through inhibition of COX-1.

A prior prospective experimental outcome study [53] of complicated upper GI events associated with nonselective NSAIDs (MUCOSA study) reported that 0.95% of RA patients had complicated upper GI events over 6 months. The MUCOSA study demonstrated that misoprostol decreased the risk of these complicated events by approximately 40% over 6 months [53]. The incidence of complicated upper GI events in the NSAID arm of the MUCOSA study is comparable to the 6-month cumulative incidence of complicated upper GI events in the naproxen treatment group in VIGOR (0.75%; see Figure 2). The 40% risk reduction in complicated upper GI events associated with misoprostol at 6 months is numerically less than the 67% relative risk reduction of complicated upper GI events seen with rofecoxib at 6 months in VIGOR (Figure 2), however a head-to-head comparison would be needed to determine if this difference is significant.

The VIGOR data compare favorably with epidemiologic data for the risk of clinical upper GI events in users of nonselective NSAIDs. Meta-analyses by Gabriel *et al*. [5] and Bollini *et al*. [54] indicated that the relative risk of complicated upper GI Events is increased 2.74- [5] to 3.5-fold [54] for NSAID users as compared with non-users. Among the different nonselective NSAIDs, the relative risk of complicated upper GI events in naproxen users versus non-NSAID users was estimated to be 2.84, with a 95% CI of (1.68, 4.82) [5]. The relative risk in VIGOR of confirmed, complicated upper GI events for naproxen users relative to rofecoxib users was 2.33 with a 95% CI of (1.28, 4.17) (these relative risk and confidence intervals are the reciprocals of the respective values shown in Section 2.4.1.2 for rofecoxib users versus naproxen users). In these meta-analyses [5; 54], however, attempts were made to exclude events that had confounding causes. In VIGOR, the relative risk of confirmed, complicated upper GI events without confounding causes for naproxen users relative to rofecoxib users was 2.78 with a 95% CI of (1.47, 5.26) (Section 2.4.1.5 Per-Protocol and Sensitivity Analyses). These data from the published meta-analyses and VIGOR are consistent and imply that the incidence of clinically important gastrointestinal adverse events in patients taking rofecoxib approach the expected background incidence in the population not using NSAIDs.

In summary, the GI safety program for rofecoxib consisted of a range of studies to precisely and conclusively test the GI component of the COX-2 hypothesis. These included mechanistic studies that examined the impact of rofecoxib or nonselective COX-1/COX-2 inhibitors on gastric mucosal COX activity, endoscopic surveillance studies designed to maximize the sensitivity and the precision of the detection of upper GI ulceration following therapy with rofecoxib or nonselective NSAIDs, a combined analysis of clinical upper GI events in OA patients, and a large clinical GI outcomes study in RA patients (VIGOR) to definitively and precisely measure the impact of therapy with rofecoxib versus nonselective NSAIDs on clinical upper GI events

associated with NSAID gastropathy. The results of these studies are remarkably consistent. In the mechanistic studies, therapy with nonselective NSAIDs, but not rofecoxib at 25 mg and 50 mg daily, reduced gastric COX activity, a function that is necessary for the maintenance of gastric homeostasis. In the endoscopic studies, therapy with rofecoxib was associated with a substantial reduction in symptomatic and asymptomatic erosions and ulcers. Finally, and most conclusively, therapy with a dose of rofecoxib averaging ~25 mg daily in the combined OA analysis and with rofecoxib 50 mg daily in VIGOR, a dose that is 2 to 4 times the dose approved for chronic therapy, was found to result in a 54 to 55% reduction in the incidence of clinical upper GI events compared with nonselective NSAIDs in the 2 studies, a 57% reduction in complicated upper GI events, and a 62% reduction in GI bleeds in VIGOR. Taken together, the GI safety program has conclusively demonstrated the improved GI safety profile of rofecoxib relative to nonselective NSAID and has confirmed the GI component of the COX-2 hypothesis.

3.8 Overall Conclusions—GI Safety of Rofecoxib

- In RA patients, rofecoxib 50 mg daily (2 to 4 times the recommended dose in OA and twice the anticipated dose in RA) is associated with significantly fewer clinical upper GI events, complicated upper GI Events, and GI bleeding than 1000 mg daily of the nonselective NSAID naproxen. The risk reduction with rofecoxib in VIGOR ranged from 54% for confirmed clinical upper GI events to 62% for any GI bleed.
- In OA patients, rofecoxib at an average dose of 24.7 mg daily, is associated with significantly fewer clinical upper GI events than nonselective NSAIDs. The risk reduction with rofecoxib in the combined analysis of all Phase IIb/III OA studies was 55%.
- Rofecoxib 25 mg and 50 mg daily are associated with significantly fewer endoscopic ulcers in OA patients than ibuprofen 2400 mg daily.
- The improved GI safety of rofecoxib compared with nonselective NSAIDs is observed in the entire OA and RA patient populations and in high-risk subgroups, including the elderly, corticosteroid users, and patients with a prior history of a clinical upper GI event. Consistency of effect is also maintained in subgroups defined by age, gender, and race.
- These broad findings in different studies, at different doses, and in both OA and RA populations indicate that the improved GI safety of rofecoxib relative to nonselective NSAIDs applies generally to patients who require chronic therapy with NSAIDs.
- In postmarketing experience, the incidence of clinical upper GI events and complicated upper GI events is low and consistent with their expected background rates in patients not exposed to NSAIDs.

The high degree of consistency throughout all studies in the GI safety program and the nearly identical reduction in the relative risk of clinical upper GI events and complicated

upper GI events in the combined analysis of the Phase IIb/III OA program and in VIGOR speaks strongly for the robustness of these data and confirms the conclusions of the individual studies. Thus, overall, it is concluded:

- Rofecoxib, a highly selective COX-2 inhibitor, provides efficacy similar to nonselective NSAIDs but with significantly less gastropathy, significantly fewer clinical upper GI events, and significantly fewer complicated upper GI events than nonselective NSAIDs.

These results support deletion of the NSAID-class GI *Warning* from the rofecoxib U.S. Product Circular and a description of the GI effects in the label.

4. General Safety of Rofecoxib

4.1 Introduction and Organization of the General Safety Presentation

VIGOR represented an opportunity to explore further the safety of rofecoxib at doses 2 to 4 times the chronic doses (12.5 mg and 25 mg) currently approved for OA and twice the anticipated dose for RA. The primary safety data in the original NDA for rofecoxib were derived from the study of approximately 3600 OA patients participating in Phases II to III studies and encompassed over 2100 patient-years of treatment. A total of 1385 patients received rofecoxib for 6 months or longer; 818 received rofecoxib for 1 year or longer. These studies included patients exposed to doses of rofecoxib indicated for chronic use, 12.5 mg and 25 mg, as well as patients that received rofecoxib 50 mg. Overall, therapy with rofecoxib was found to be generally well-tolerated. The safety profile of rofecoxib in these clinical studies was shown to be favorable in comparison to nonselective NSAIDs. Adverse experiences associated with rofecoxib represent a subset of those described for the nonselective NSAIDs and numerically the incidence of these non-GI events with rofecoxib is similar to the incidence with nonselective NSAIDs dosed at comparable points on their efficacy dose-response curves. Thus, consistent with the inhibition of COX-2, rofecoxib was associated with renal/vascular adverse effects (hypertension and edema) similar to nonselective NSAIDs. In addition, approximately 1% of patients taking rofecoxib 12.5 or 25 mg experienced elevations in liver transaminases that were ≥3 times the upper limit of normal. In the OA studies, these elevations resolved in patients treated with rofecoxib, with approximately half resolving while patients remained on therapy. These effects on liver function were similar to ibuprofen and significantly less than diclofenac.

The safety profile of a drug is best determined from placebo-controlled studies and the primary analysis of rofecoxib safety in OA patients was based on placebo-controlled data. A placebo comparator was not included in VIGOR. An alternative approach is to compare adverse experiences of a drug with those of a comparably-dosed active comparator. However, in order to rigorously evaluate the GI safety hypothesis, the VIGOR study used 50 mg rofecoxib (2 times the anticipated maximum chronic dose of rofecoxib) and less than the maximum approved dose of naproxen (1000 mg). Thus, the interpretation of adverse experiences in the VIGOR study is complicated because there is neither a placebo control group nor a comparably-dosed active comparator group in the study. The comparison of adverse experience rates in this study must be made with the understanding that a relative increase in mechanism-based, dose-dependent adverse experiences for rofecoxib 50 mg compared with naproxen 1000 mg would therefore be expected.

The general safety of rofecoxib in VIGOR is presented in Section 4.2. Overall, the adverse experience profile of rofecoxib in this study was consistent both qualitatively and quantitatively with the previous experience in OA and with the approved U.S. Product Circular for rofecoxib. Thus, some patients in VIGOR had adverse experiences of hypertension or edema. In general, these episodes did not require discontinuation of

study drug. The incidence of hypertension and edema in patients taking rofecoxib 50 mg in VIGOR were similar or lower than the 50-mg group in the OA studies. Differences between rofecoxib and naproxen in the incidence of these dose-dependent adverse experiences in VIGOR were likely a function of the disparity in doses used in this study. Hepatic-related adverse experiences with rofecoxib in VIGOR were infrequent and consistent with approved labeling; less than 1% of patients had elevations in alanine aminotransferase or aspartate aminotransferase that were ≥3 times the upper limit of normal. The general safety analysis (Section 4.2) provides these results in greater detail. The new data from VIGOR are consistent with previous data obtained in OA patients as reported in the original NDA and as reflected in the rofecoxib U.S. Product Circular.

One area of difference between the rofecoxib and naproxen groups in VIGOR that required additional exploration was the incidence of thrombotic cardiovascular events. In contrast to the results presented at the previous Advisory Committee Meeting from the OA studies (in which rofecoxib was compared with diclofenac, ibuprofen, and nabumetone), in VIGOR there was a statistically significant difference in the incidence of thrombotic cardiovascular serious adverse experiences between the rofecoxib and naproxen groups. A review of rofecoxib safety with regard to thrombotic cardiovascular serious adverse experiences is presented in Section 4.3. This review includes data from clinical pharmacology studies that investigated the effects of COX-2 selective inhibitors and nonselective NSAIDs on platelet function and on prostacyclin production, the data from VIGOR, and data from rofecoxib clinical studies that provide information on the risk of thrombotic cardiovascular serious adverse experiences in patients taking rofecoxib, placebo, or non-naproxen, nonselective NSAIDs. In these other studies, the incidence of thrombotic cardiovascular serious adverse experiences was similar in patients taking rofecoxib, placebo, or non-naproxen, nonselective NSAIDs.

4.2 General Safety of Rofecoxib in VIGOR

4.2.1 Overview and Introduction

The safety profile of rofecoxib was established in approximately 3600 OA patients participating in Phase II to III placebo and active-comparator controlled studies. Of these, 1385 patients received rofecoxib for 6 months or longer and 818 for 1 year or longer. The safety data from 6-week, 6-month, and 86-week studies in the original NDA are the primary sources for approved rofecoxib safety labeling.

The approved chronic doses of rofecoxib for OA are 12.5 mg and 25 mg and the anticipated dose for the treatment of RA is 25 mg. The approved label for rofecoxib provides safety information for the approved doses and for the 50-mg dose. A daily dose of 50 mg is 2 to 4 times the approved dose for chronic use. Systemic exposure, based on pharmacokinetics, reveals the dose proportionality of rofecoxib over the 12.5- to 100-mg dose range. Thus, 50 mg rofecoxib would be associated with 2 to 4 times the systemic exposure of the approved chronic doses of rofecoxib.

Most of the 50-mg safety data in the original NDA and in the approved rofecoxib label comes from the Phase III Placebo-Controlled 6-Month OA endoscopy studies; 379 patients were assigned to receive 50 mg rofecoxib in these 6-month studies (mean duration of exposure = 4.7 months).

General safety data from VIGOR represent confirmatory information for the 50-mg daily dose of rofecoxib. The mean duration of time on study therapy in VIGOR (8 months) was longer than the experience with 50 mg in the OA studies. Nonetheless, the specific adverse experience rates were generally similar or lower in VIGOR compared to the Phase III Placebo-Controlled 6-Month OA Studies and were consistent with the currently approved labeling [Appendix 3 Approved U.S. Product Circular for Rofecoxib].

This review of the general safety of rofecoxib in VIGOR will focus on both quantitative and qualitative comparisons in adverse experiences between patients treated with rofecoxib 50 mg in VIGOR and patients treated with rofecoxib in previous studies submitted as part of the original NDA and as reflected in the rofecoxib product circular.

The analysis of safety data is essentially a screening process. Statistical testing helps identify outcomes that may require further clinical assessment. To minimize problems associated with interpretation of multiple statistical tests, statistical significance testing (that is, the calculation of a “p” value) was only performed on those adverse experiences for which significance testing was prespecified. For the prespecified adverse experiences, a “p” value on the difference in relative risk between the rofecoxib and naproxen groups is provided. For other adverse experiences, only the incidence rates are reported.

The adverse experiences terms for which statistical significance testing was prespecified and the sections in which each is discussed are:

- Discontinuations due to digestive adverse experiences including abdominal pain (Section 2.4.1.7).
- Drug-related (possibly, probably, definitely) clinical adverse experiences (overall) (Section 4.2.2).
- Serious clinical adverse experiences (overall) (Section 4.2.3).
- Clinical adverse experiences leading to study discontinuation (overall) (Section 4.2.3).
- Serious laboratory adverse experiences (overall) (Section 4.2.4).
- Drug-related (possibly, probably, definitely) laboratory adverse experiences (overall) (Section 4.2.4).
- Laboratory adverse experiences leading to study discontinuation (overall) (Section 4.2.4).
- Discontinuations due to edema-related adverse experiences (Section 4.2.5.1).
- Discontinuations due to hypertension-related adverse experiences (Section 4.2.5.1).

- Discontinuations due to renal-related adverse experiences (clinical and/or laboratory adverse experiences) (Section 4.2.5.1).
- Congestive heart failure adverse experiences (Section 4.2.5.1).
- Discontinuations due to hepatic-related adverse experiences (clinical and/or laboratory adverse experiences) (Section 4.2.5.3).

Clinical interpretation of these statistical tests must be viewed in the context of the dosage disparity between rofecoxib and naproxen that was designed into the study and the multiplicity of statistical comparisons.

4.2.2 Clinical Adverse Experiences

Table 10 provides a summary of the clinical adverse experiences observed in VIGOR. Overall, rofecoxib was very well tolerated. As shown in Table 10, the overall incidence of discontinuations due to clinical adverse experiences was similar between treatment groups (approximately 16% in both treatment groups). The most common adverse experiences leading to discontinuation were all related to the digestive system. These were discussed in Section 2.4.1.7.

Drug-related adverse experiences (those assessed by the investigator to have been possibly, probably or definitely related to study therapy) occurred in 34.5% of patients taking rofecoxib and 36.1% of patients taking naproxen (p=0.238 for prespecified test of difference in relative risk between groups). No meaningful clinical or statistical differences were observed between the 2 groups.

Table 10

VIGOR Study
Clinical Adverse Experience Summary

Number (%) of patients:	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
With one or more adverse experiences	2872	(71.0)	2824	(70.1)
With no adverse experience	1175	(29.0)	1205	(29.9)
With drug-related adverse experiences†	1395	(34.5)	1456	(36.1)
With serious adverse experiences	378	(9.3)	315	(7.8)
With serious drug-related adverse experiences†	51	(1.3)	80	(2.0)
Who died	22	(0.5)	15	(0.4)
Discontinued due to adverse experiences	643	(15.9)	635	(15.8)
Discontinued due to drug-related adverse experiences†	456	(11.3)	520	(12.9)
Discontinued due to serious adverse experiences	143	(3.5)	127	(3.2)
Discontinued due to serious drug-related adverse experiences†	35	(0.9)	68	(1.7)

† Assessed by the investigator to be possibly, probably, or definitely drug related.

Table 11 presents specific adverse experiences with an incidence of at least 2% in any treatment group. A cutoff of 2% was chosen for consistency with the approved U.S. Product Circular. An individual patient is counted only once for each body system (e.g., "cardiovascular") where he/she reported one or more adverse experiences. However, for each specific adverse experience term (e.g., "hypertension") the total number of patients reporting that experience is recorded. The most commonly reported adverse experiences were digestive system adverse experiences. Overall the incidences of specific adverse experiences in VIGOR were similar to or less than the incidences reported with 50 mg rofecoxib in the 6-Month OA studies and consistent with approved labeling. The adverse experiences hypertension, edema, and rash are discussed in greater detail in Section 4.2.5.2.

Table 11

VIGOR Study
Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence ≥2% in One or More Treatment Groups) by Body System

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Patients with one or more adverse experience	2872	(71.0)	2824	(70.1)
Patients with no adverse experience	1175	(29.0)	1205	(29.9)
Body As A Whole/Site Unspecified	**1071**	**(26.5)**	**1003**	**(24.9)**
Abdominal Pain	158	(3.9)	189	(4.7)
Dizziness	118	(2.9)	85	(2.1)
Influenza-Like Disease	121	(3.0)	114	(2.8)
Lower Extremity Edema	161	(4.0)	104	(2.6)
Upper Respiratory Infection	240	(5.9)	248	(6.2)
Cardiovascular System	**590**	**(14.6)**	**390**	**(9.7)**
Hypertension	342	(8.5)	202	(5.0)
Digestive System	**1320**	**(32.6)**	**1449**	**(36.0)**
Constipation	63	(1.6)	114	(2.8)
Diarrhea	254	(6.3)	206	(5.1)
Dyspepsia	212	(5.2)	259	(6.4)
Epigastric Discomfort	197	(4.9)	274	(6.8)
Heartburn	197	(4.9)	194	(4.8)
Nausea	268	(6.6)	217	(5.4)
Vomiting	91	(2.2)	84	(2.1)
Eyes, Ears, Nose, And Throat	**450**	**(11.1)**	**397**	**(9.9)**
Pharyngitis	83	(2.1)	73	(1.8)
Sinusitis	86	(2.1)	93	(2.3)
Metabolism And Nutrition[†]	**128**	**(3.2)**	**132**	**(3.3)**
Musculoskeletal System	**630**	**(15.6)**	**613**	**(15.2)**
Back Pain	74	(1.8)	83	(2.1)
Rheumatoid Arthritis	190	(4.7)	170	(4.2)

Table 11 (Cont.)

VIGOR Study
Number (%) of Patients With Specific Clinical Adverse Experiences
(Incidence ≥2% in One or More Treatment Groups) by Body System

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Nervous System[†]	**456**	**(11.3)**	**356**	**(8.8)**
Psychiatric Disorder[†]	**108**	**(2.7)**	**92**	**(2.3)**
Respiratory System	**346**	**(8.5)**	**343**	**(8.5)**
Bronchitis	115	(2.8)	131	(3.3)
Skin And Skin Appendages	**508**	**(12.6)**	**410**	**(10.2)**
Rash	142	(3.5)	119	(3.0)
Urogenital System	**372**	**(9.2)**	**341**	**(8.5)**
Urinary Tract Infection	172	(4.3)	187	(4.6)

[†] Individual adverse experience terms within these body systems occurred in <2% patients in either group.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

4.2.3 Serious Adverse Experiences and Discontinuations

Fatal and Nonfatal Serious Adverse Experiences

The incidence of serious adverse experiences was 9.3% and 7.8% on rofecoxib and naproxen, respectively (Table 12) (p=0.013 for prespecified test of difference in relative risk between groups). In contrast, the incidence of drug-related serious adverse experiences was greater on naproxen compared with rofecoxib (0.9% on rofecoxib versus 1.7% on naproxen). The incidence of serious adverse experiences was similar in all body systems, except for the cardiovascular (2.5% on rofecoxib versus 1.1% on naproxen) and digestive (1.2% on rofecoxib versus 2.4% on naproxen) body systems.

Of the serious digestive system adverse experiences, 22 (0.5%) in the rofecoxib group and 67 (1.7%) in the naproxen group, were related to either a clinical upper GI event or a

lower GI bleed. The remaining 26 (0.6%) in the rofecoxib group and 30 (0.8%) in the naproxen group were serious but were not related to either a clinical upper GI event or lower GI bleed.

Cardiovascular system serious adverse experiences occurred more frequently with rofecoxib compared with naproxen (2.5% versus 1.1%). This finding is largely accounted for by differences between the groups in the incidence of certain cardiovascular serious adverse experiences: myocardial infarction (0.5% versus 0.1%), congestive heart failure (0.3% versus 0.1%), and cerebrovascular accident (0.3% versus 0.1%) (Table 12). Congestive heart failure is discussed in Section 4.2.5.1. Thrombotic cardiovascular serious adverse experiences are more thoroughly discussed in Section 4.3.

Table 12

VIGOR Study
Number (%) of Patients With Specific Fatal and Nonfatal Serious Clinical Adverse Experiences by Body System

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Patients with one or more adverse experience	378	(9.3)	315	(7.8)
Patients with no adverse experience	3669	(90.7)	3714	(92.2)
Body As A Whole/Site Unspecified	51	(1.3)	35	(0.9)
Cardiovascular System	101	(2.5)	46	(1.1)
Digestive System	48	(1.2)	97	(2.4)
Endocrine System	4	(0.1)	0	(0.0)
Eyes, Ears, Nose, And Throat	13	(0.3)	4	(0.1)
Hemic And Lymphatic System	8	(0.2)	7	(0.2)
Hepatobiliary System	11	(0.3)	8	(0.2)
Immune System	1	(0.0)	1	(0.0)
Metabolism And Nutrition	2	(0.0)	3	(0.1)
Musculoskeletal System	83	(2.1)	70	(1.7)
Nervous System	14	(0.3)	7	(0.2)
Psychiatric Disorder	7	(0.2)	3	(0.1)
Respiratory System	52	(1.3)	39	(1.0)
Skin And Skin Appendages	32	(0.8)	20	(0.5)
Urogenital System	32	(0.8)	23	(0.6)

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a body system. The same patient may appear in different body systems.

Thirty-seven deaths occurred in the trial, 22 (0.5%) in the rofecoxib group and 15 (0.4%) in the naproxen group. The most common cause of death in both the rofecoxib and naproxen treatment groups was pneumonia (4 patients each). Overall, the observed incidence of fatal clinical adverse experiences by body system as well as the incidence of individual fatal clinical adverse experiences were similar between treatment groups.

Discontinuations Due to Clinical Adverse Experiences

Table 13 summarizes by body system the most frequent clinical adverse experiences that led to study discontinuation. One thousand two hundred seventy-eight (15.8%) patients discontinued due to a clinical adverse experience, 15.9% in the rofecoxib group and 15.8% in the naproxen group (p=0.842 for prespecified test of difference in relative risk between groups) (Table 13). The most common reasons for discontinuation were all digestive system adverse experiences: abdominal pain (0.6% rofecoxib versus 1.2% naproxen), diarrhea (0.7% rofecoxib versus 0.4% naproxen), dyspepsia (1.1% rofecoxib versus 1.4% naproxen), epigastric discomfort (0.5% rofecoxib versus 1.2% naproxen), gastric ulcer (0.4% rofecoxib versus 1.4% naproxen), heartburn (0.7% rofecoxib versus 0.7% naproxen), and nausea (0.8% rofecoxib versus 0.8% naproxen) (see Section 2.4.1.7). The rate of discontinuations due to any digestive system adverse experience was significantly lower in patients treated with rofecoxib 50 mg than in patients treated with naproxen. The total number of patients who discontinued due to upper GI symptom adverse experiences (i.e., dyspepsia, abdominal pain, epigastric discomfort, nausea, and heartburn) was 142 (3.5%) in the rofecoxib and 196 (4.9%) in the naproxen group. Differences in cardiovascular system adverse experiences are considered below in Section 4.2.5 Adverse Experiences of Special Interest and in Section 4.3.4 Analysis of Cardiovascular Events.

Table 13

VIGOR Study
Number (%) of Patients Discontinued Due to Specific Clinical Adverse Experiences by Body System

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Patients with one or more adverse experience	643	(15.9)	635	(15.8)
Patients with no adverse experience	3404	(84.1)	3394	(84.2)
Body As A Whole/Site Unspecified	100	(2.5)	107	(2.7)
Cardiovascular System	109	(2.7)	33	(0.8)
Digestive System	292	(7.2)	392	(9.7)
Endocrine System	0	(0.0)	2	(0.0)
Eyes, Ears, Nose, And Throat	20	(0.5)	11	(0.3)
Hemic And Lymphatic System	4	(0.1)	9	(0.2)
Hepatobiliary System	10	(0.2)	2	(0.0)
Immune System	6	(0.1)	5	(0.1)
Metabolism And Nutrition	5	(0.1)	6	(0.1)
Musculoskeletal System	29	(0.7)	27	(0.7)
Nervous System	44	(1.1)	24	(0.6)
Psychiatric Disorder	3	(0.1)	10	(0.2)
Respiratory System	23	(0.6)	13	(0.3)
Skin And Skin Appendages	42	(1.0)	37	(0.9)
Urogenital System	17	(0.4)	9	(0.2)

Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

4.2.4 Laboratory Adverse Experiences

Overall, the incidence of laboratory adverse experiences was similar between the 2 treatment groups (Table 14). Laboratory adverse experiences were reported much less frequently than clinical adverse experiences, occurring in 10.4% of patients in the rofecoxib group and 9.2% of patients in the naproxen group. Considering the dosage disparity, it is notable that there were no clinically meaningful differences between the groups.

Table 14

VIGOR Study
Laboratory Adverse Experience Summary

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)†	n	(%)†
With at least one laboratory test postbaseline	4006		3999	
Number (%) of patients:				
With one or more adverse experiences	418	(10.4)	368	(9.2)
With no adverse experience	3588	(89.6)	3631	(90.8)
With drug-related‡ adverse experiences	191	(4.8)	173	(4.3)
With serious adverse experiences	2	(0.0)	0	(0.0)
With serious drug-related‡ adverse experiences	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	22	(0.5)	12	(0.3)
Discontinued due to drug-related‡ adverse experiences	20	(0.5)	10	(0.3)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related‡ adverse experiences	0	(0.0)	0	(0.0)

† The percent = number of patients within the laboratory adverse experience category/number of patients with one or more laboratory tests postbaseline.
‡ Assessed by the investigator to be possibly, probably or definitely drug related.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a body system. The same patient may appear in different body systems.

Drug-related laboratory adverse experiences occurred in less than 5% of patients in each treatment group and there were no clinically meaningful differences between the groups (p=0.309 for prespecified test of difference in relative risk between groups).

The incidence of patients who discontinued due to a laboratory adverse experience and the incidence of patients who discontinued due to a drug-related (assessed by the investigator as either possibly, probably or definitely related to study therapy) laboratory adverse experience were both low and similar in the rofecoxib and naproxen groups (for patients discontinued due to a laboratory adverse experience, p=0.091 for prespecified test of difference in relative risk between groups.)

Serious laboratory adverse experiences occurred in only 2 patients (rofecoxib group) (p=0.154 for prespecified test of difference in relative risk between groups.) A 57-year-old woman who had been taking methotrexate 10 mg/week was hospitalized for

neutropenia 1 week after completing the protocol and a 62-year-old woman whose dose of methotrexate was increased from 10 to 15 mg weekly subsequently developed leukopenia and decreased platelets. In both cases, the adverse experiences were thought to be due to concurrent methotrexate therapy and were rated by the investigators as not related to therapy with study drug. No other differences in the overall incidence of laboratory adverse experiences were observed between patients taking or not taking concomitant methotrexate for RA.

4.2.5 Adverse Experiences of Special Interest

NSAIDs have been associated with both renal and hepatic toxicity. In many instances these effects are transient and resolve on therapy. To evaluate the clinical impact of these effects, renal and hepatic adverse experiences which resulted in discontinuation of the patient from the study or in an important clinical syndrome (i.e., congestive heart failure) were evaluated in a prespecified manner.

4.2.5.1 Adverse Experiences Related to Renal Function

Renal adverse experiences commonly associated with the use of NSAIDs include reductions in glomerular filtration rate and reductions in the renal excretion of sodium with the potential for fluid retention and edema, and hypertension [55; 56]. These adverse experiences are mechanism-based and dose related; that is, the incidence of these adverse experiences increases with higher doses of NSAIDs [57]. The magnitude of the clinical impact of these effects in VIGOR was evaluated in the prespecified analyses presented below.

It is important to emphasize that the safety data from VIGOR pertain to a dose of rofecoxib (50 mg) that is 2 to 4 times higher than the approved chronic dose for OA and 2 times the anticipated dose for RA whereas the dose of naproxen (1000 mg) is less than the maximal approved dose. Therefore, a relative increase in mechanism-based, dose-dependent adverse experiences for rofecoxib 50 mg compared with naproxen 1000 mg would be expected. In contrast to this analysis of rofecoxib 50 mg in VIGOR, the incidences of renal adverse experiences including edema and hypertension are similar for rofecoxib and nonselective NSAIDs when dosed at similar points on their efficacy dose-response curves. As shown in the approved U.S. Product Circular for rofecoxib [Appendix 3], the incidence of lower extremity edema in 6-week to 6-month OA studies was 3.7% in patients taking rofecoxib (12.5 mg or 25 mg daily), 3.8% in patients taking ibuprofen (2400 mg daily) and 3.4% in patients taking diclofenac (150 mg daily), The incidence of hypertension in 6-week to 6-month OA studies was 3.5% in patients taking rofecoxib, 3.0% in patients taking ibuprofen and 1.6% in patients taking diclofenac.

Edema-Related Adverse Experiences

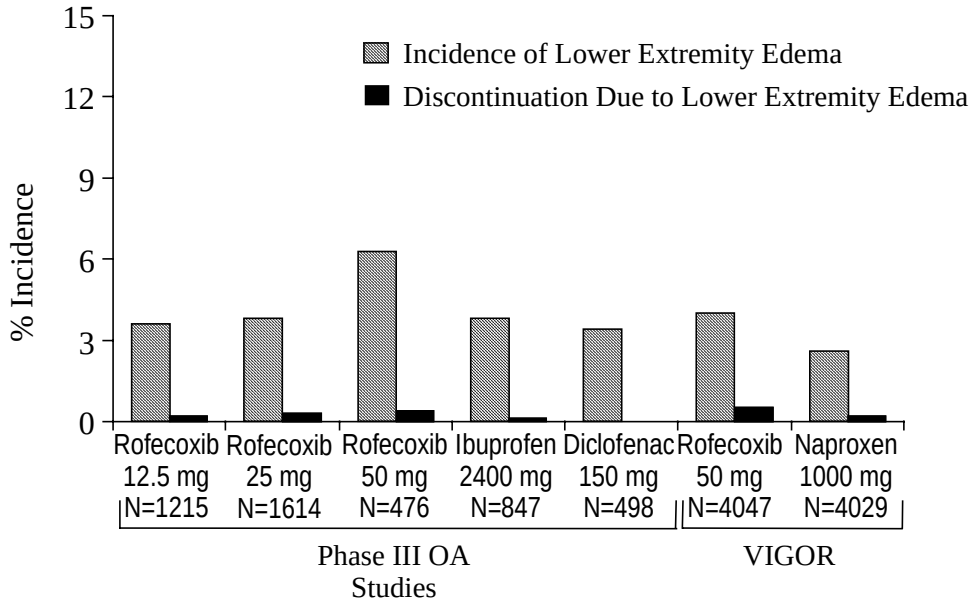
Discontinuation due to edema-related adverse experiences was prespecified as the primary approach to analyze the clinical importance of this adverse experience in VIGOR. Predefined edema-related adverse experiences reported in this study included edema, peripheral edema, lower extremity edema, and fluid retention. Less than 1% of

patients discontinued for an edema-related adverse experience: 0.6% of patients in the rofecoxib group and 0.3% of patients in the naproxen group (p=0.057 for prespecified test of difference in relative risk between groups).

The most common edema-related adverse event was lower-extremity edema. However, the incidence of lower-extremity edema in VIGOR (4.0% in the rofecoxib group and 2.6% in the naproxen group) was lower than that reported for the 50-mg dose in the 6-week to 6-month studies described in the approved U.S. Product Circular (6.3%) (Figure 8 and Appendix 3).

Figure 8

Lower Extremity Edema Incidence and Discontinuation Rates
VIGOR Study Versus Phase IIb/III OA Studies
(From U.S. Product Circular 6-Week to 6-Month Studies)



Hypertension-Related Adverse Experiences

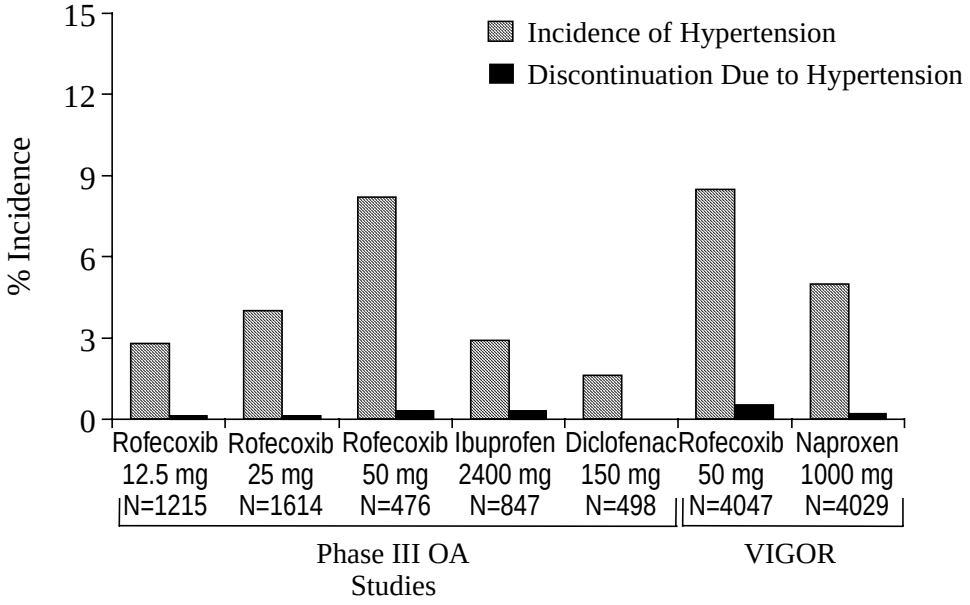
Discontinuation due to hypertension-related adverse experiences was prespecified as the primary approach to analyze the clinical importance of this adverse experience in VIGOR. Hypertension-related adverse experiences reported in this study included the terms: blood pressure increased, borderline hypertension, diastolic hypertension, hypertension, hypertension uncontrolled with medication, hypertensive crisis, labile hypertension, systolic hypertension, and uncontrolled hypertension. No patient

experienced malignant hypertension. The discontinuation of a patient due to a hypertension-related adverse experience was uncommon in both treatment groups, however, the rate was significantly higher in patients treated with rofecoxib (0.7%) compared to naproxen (0.1%) ($p<0.001$).

The most frequently occurring hypertension-related adverse experience in this study was the adverse experience term "hypertension" (8.5% in the rofecoxib group and 5.0% in the naproxen group). The incidence of hypertension adverse experiences in the rofecoxib group in VIGOR was similar to that reported for the 50-mg dose in the 6-week to 6-month studies described in the approved U.S. Product Circular (8.2%) (Figure 9 and Appendix 3).

Figure 9

Hypertension Incidence and Discontinuation Rates
VIGOR Study Versus Phase IIb/III OA Studies
(From U.S. Product Circular 6-Week to 6-Month Studies)



Data on blood pressure measurements were also collected in VIGOR. The mean systolic blood pressure in patients taking rofecoxib 50 mg was 133.2 mm Hg; this corresponded to a 4.6 mm Hg mean increase in systolic blood pressure from baseline. The mean systolic blood pressure in patients taking naproxen 1000 mg was 129.8 mm Hg; this corresponded to a 1.0 mm Hg increase. For both rofecoxib and naproxen, there were

smaller increases from baseline in diastolic blood pressure (1.7 mm Hg for rofecoxib 50 mg and 0.1 mm Hg for naproxen 1000 mg). The baseline in this study was after the 3-day NSAID washout.

In contrast to these data for rofecoxib 50 mg in VIGOR, data from Phase IIb/III OA studies in the original NDA show that, at approved doses for chronic use (12.5 and 25 mg), mean systolic and diastolic blood pressure in patients taking rofecoxib were similar to the mean values in patients taking nonselective NSAIDs and to the values at screening (before patients had discontinued their baseline NSAID therapy). Compared to baseline (when patients were off NSAIDs), rofecoxib 12.5 mg and 25 mg were associated with mean increases in diastolic blood pressure of 0.5 to 1.0 mm Hg and increases in systolic blood pressure of approximately 1 to 3 mm Hg. These changes for rofecoxib 12.5 mg and 25 mg were similar to those for the nonselective NSAID comparators.

Adverse Experiences of Congestive Heart Failure

Although rare, congestive heart failure is one of the more clinically significant manifestations of the fluid retention that can be caused by selective COX-2 or dual COX-1/COX-2 inhibitors. Therefore, an analysis of all adverse experiences of congestive heart failure was one of the prespecified clinical adverse experience categories. Congestive heart failure occurred in 19 (0.5%) patients in the rofecoxib group and 9 (0.2%) patients in the naproxen group. The overall incidence of these events was very low and similar to that observed with rofecoxib 50 mg in the original NDA (0.6%). The rate of congestive heart failure adverse experiences was not statistically significantly different between the 2 treatment groups (p=0.065 for prespecified test of difference in relative risk between groups.) Six (0.1%) patients, all in the rofecoxib group, discontinued due to congestive heart failure.

Other Renal-Related Adverse Experiences

NSAIDs have been reported to cause decreases in glomerular filtration rate (GFR) that sometimes result in overt renal decompensation. Discontinuations due to renal-related adverse experiences (clinical and laboratory combined) was prespecified as the primary approach to analyze the clinical importance of these adverse experiences in VIGOR. Renal-related adverse experiences reported in this study included: increased serum creatinine, increased blood urea nitrogen, renal failure, and renal insufficiency. Adverse experiences related to measures of GFR were extremely rare and similar between treatment groups. Eight patients in the rofecoxib treatment group and 7 patients in the naproxen treatment group discontinued due to a renal-related adverse experience (p=0.796 for prespecified test of difference in relative risk between groups). There was 1 patient on rofecoxib and 4 patients on naproxen who had serious renal-related adverse experiences. Two renal-related serious adverse experiences (both on naproxen) were considered drug-related.

In addition to the above adverse experiences related to glomerular filtration rate, there were 3 serious adverse experiences reported (nephrotic syndrome [rofecoxib], interstitial

nephritis [naproxen] and proteinuria [naproxen]) not considered part of the renal-related adverse experiences analyses. Both the patient with nephrotic syndrome and the patient with proteinuria were taking concomitant gold therapy. There were no cases of papillary necrosis.

The most frequently reported renal-related adverse experience in both groups was increased serum creatinine, which was reported in 1.0% of the patients in the rofecoxib group and 0.7% of patients in the naproxen group. The majority resolved while the patients continued on therapy.

4.2.5.2 Allergic Reactions in VIGOR

Allergic reactions are a well-described adverse experience with NSAIDs. The incidence of rash was similar in the rofecoxib and naproxen groups (3.5% and 3.0%, respectively). Most episodes in both treatment groups were transient, self-limited, and resolved while study therapy was continued. The incidence of patients with drug-related episodes of rash was similar between treatment groups (54 [1.3%] for the rofecoxib group and 44 [1.1%] for the naproxen group). Most importantly, few patients in the rofecoxib and naproxen groups discontinued because of rash, with the incidence of discontinuations for rash almost identical in the 2 treatment groups (17 [0.4%] for the rofecoxib group and 19 [0.5%] for the naproxen group). The incidence of rash with rofecoxib in this study was also consistent with the 6-Month Osteoarthritis Studies for the 50-mg rofecoxib group (2.9%).

Hypersensitivity reactions occurred in 170 (4.2%) patients in the rofecoxib group and 153 (3.8%) patients in the naproxen group. The following terms were considered hypersensitivity reactions: anaphylaxis, erythema multiforme minor, immediate hypersensitivity, morbilliform rash, Stevens-Johnson syndrome, vesiculobullous rash, anaphylactic reaction, anaphylactic shock, anaphylactoid reaction, exanthema, hypersensitivity reaction, rash, urticaria, sulfonamide allergy, and sulfa allergy. Twenty-six (26) patients in the rofecoxib group discontinued due to a hypersensitivity allergic experience; 30 patients in the naproxen group discontinued due to a hypersensitivity allergic experience. Thus, the incidence of hypersensitivity reactions in VIGOR was similar in patients taking rofecoxib and naproxen.

4.2.5.3 Clinical and Laboratory Adverse Experiences Related to Alterations in Liver Function

Discontinuations due to hepatic-related adverse experiences was prespecified as the primary approach to analyze the clinical importance of this adverse experience in VIGOR. Hepatic-related adverse experiences reported in this study included: increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), hepatic disorder, hepatic failure, hepatic function abnormality, hepatitis, and jaundice. The number of patients who discontinued from the study for hepatic-related adverse experiences was low: 10 (0.2%) in the 50-mg rofecoxib and 3 (0.1%) in the 1000-mg naproxen groups (p=0.067).

The overall incidence of increased ALT adverse experiences was 1.8% for the rofecoxib and 1.0% for the naproxen groups. The overall incidence of increased ALT adverse experiences in the rofecoxib group in this study was lower than that reported in the original NDA (6-Month OA Studies) for the 50-mg rofecoxib group (2.4%). The overall incidence of increased AST adverse experiences was 1.6% for the rofecoxib and 0.9% for the naproxen groups. The overall incidence of increased AST in the rofecoxib group in this study was lower than that reported in the original NDA (6-Month OA Studies) for the 50-mg rofecoxib group (2.7%). The majority of increased AST and ALT adverse experiences were transient, resolved on study therapy, and represented changes <3 times the upper limit of normal (ULN).

Analysis of changes in AST or ALT ≥3 times the upper limit of normal (ULN) in VIGOR showed that 0.5% of patients on rofecoxib had at least 1 single (nonconsecutive) AST value ≥3 times ULN and 0.3% had increases in ALT ≥3 times ULN. Also in VIGOR, 0.2% of patients on naproxen had at least 1 single (nonconsecutive) AST ≥3 times ULN and 0.3% had increases in ALT ≥3 times ULN. In the 6-Month OA Studies, the incidence rates of increased ALT ≥3 times ULN and increased AST ≥3 times ULN in the rofecoxib group were similar to the rates in the ibuprofen group and significantly less than the rates in the diclofenac group. The rofecoxib rates in VIGOR are consistent with currently approved labeling.

4.2.6 General Safety in VIGOR–Discussion

Phase III OA studies presented in the original NDA showed that the incidence of edema and hypertension adverse experiences are dose-related for rofecoxib, as has been described for all NSAIDs. This is consistent with the observation that systemic exposure to rofecoxib, based on plasma area-under-the-time-concentration-curve (AUC), is dose proportional over the 12.5- to 100-mg daily dose range. At the 12.5-mg and 25-mg dose, the incidence of these adverse experiences is similar to approved doses of nonselective NSAIDs.

The VIGOR study provides confirmation of the safety of rofecoxib as reported in the original NDA (6-Month OA Studies) and represented in the rofecoxib product circular. No new general safety concerns were identified. The dose of rofecoxib employed in VIGOR (50 mg once daily) is 2 to 4 times the approved dose for the treatment of OA and is anticipated to be 2 times the dose for the treatment of RA, whereas the dose of naproxen used in this study is the most commonly used dose for the treatment RA and not the maximum dose. Therefore, it was not surprising that the rates of adverse experiences that are related to inhibition of COX-2 in the kidney were higher with 50 mg rofecoxib versus 1000 mg naproxen.

4.2.7 General Safety in VIGOR—Conclusions

- The non-GI safety of rofecoxib in VIGOR was consistent both qualitatively and quantitatively with the previous experience in OA and with currently approved labeling.

- Differences between the rofecoxib 50-mg and naproxen 1000-mg group in the incidence of mechanism-based, dose-dependent adverse experiences (e.g., hypertension and edema) were consistent with the use of rofecoxib at 2 times its maximal approved dose for chronic administration.
- Discontinuations in VIGOR due to renal/vascular adverse experiences or due to alterations in laboratory measurements of liver function in patients taking rofecoxib were rare and consistent with or lower than data for rofecoxib 50 mg in approved labeling and in the Phase III 6-Month OA Studies.

4.3 Safety With Regard to Thrombotic Cardiovascular Events

4.3.1 Overview and Introduction

As discussed in detail in Section 4.3.2.1, selective COX-2 inhibitors decrease the systemic synthesis of prostacyclin without inhibiting platelet thromboxane [35; 36]. These data raised the theoretical possibility that a highly selective COX-2 inhibitor might alter the balance between these 2 prostanoids and might be prothrombotic. Alternatively, nonselective inhibitors of COX-1 and COX-2 with potent and sustained antiplatelet activity might be cardioprotective. To investigate these possibilities, an analysis of cardiovascular safety outcomes in the Phase IIb/III OA program was performed. As presented at the previous Advisory Committee Meeting and as discussed below in Section 4.3.5, patients taking rofecoxib or the comparator nonselective COX-1/COX-2 inhibitors ibuprofen, diclofenac, or nabumetone and not taking low-dose aspirin had similar incidences of thrombotic cardiovascular serious adverse experiences (only Protocol 058, a study of elderly patients 80 years or older, included a third of patients who used low-dose aspirin, 70 of whom were in the rofecoxib group).

Despite these favorable results from the OA program, it was considered important to continue to characterize the effects of rofecoxib with regard to thrombotic cardiovascular serious adverse experiences. A Cardiovascular Adjudication Standard Operating Procedure (Adjudication SOP) was developed for the Post Phase III OA rofecoxib development program more than a year prior to the initiation of VIGOR to further evaluate whether there were any differences in the incidence of these events during chronic therapy with rofecoxib versus nonselective NSAIDs or placebo. The purpose of the Adjudication SOP was: (1) to improve accuracy in diagnosis across a heterogeneous group of study investigators in different nations and having different clinical specialties; and (2) to standardize the evaluation of thrombotic cardiovascular serious adverse experiences across ongoing clinical studies of rofecoxib. A description of the Adjudication SOP and the procedures involved is in Section 4.3.3. The analysis of cardiovascular outcomes in trials of rofecoxib as described in the Adjudication SOP did not envision a separate analysis of individual trials. Individual trials would likely be underpowered with respect to subgroup and exploratory analyses necessary to understand any observed differences in event rates. Instead, the SOP was designed to examine the combined incidence of cardiovascular outcomes across a broad range of patients in all post-Phase III OA trials of rofecoxib initiated by or after the second quarter 1998.

However, based on a request from the VIGOR Data Safety Monitoring Board, a separate analysis of thrombotic cardiovascular serious adverse experiences in VIGOR was performed.

The cardiovascular results of VIGOR are presented in Section 4.3.4. In VIGOR, naproxen was associated with a 58% lower risk for the development of thrombotic cardiovascular serious adverse experiences compared with rofecoxib therapy. This difference was mostly attributable to a difference in the incidence of myocardial infarction (MI) between the groups. Whether the difference in the incidence of thrombotic cardiovascular serious adverse experiences between the rofecoxib and naproxen groups in VIGOR represented a prothrombotic effect of rofecoxib or a cardioprotective effect due to inhibition of platelet function by naproxen could not be determined by the evaluation of the VIGOR results in isolation. Therefore, a review of other rofecoxib studies as well as clinical pharmacology studies was undertaken.

As presented at the previous Advisory Committee Meeting, alluded to above, and shown here in Section 4.3.5, no difference in the incidence of thrombotic cardiovascular serious adverse experiences in VIGOR between rofecoxib and a nonselective NSAID had been seen in the Phase IIb/III OA studies. In the OA studies, patients taking rofecoxib were compared to patients taking diclofenac, ibuprofen, or nabumetone. In VIGOR, patients taking rofecoxib were compared to patients taking naproxen. Naproxen is among the few nonselective NSAIDs with potent antiplatelet effects that are sustained throughout the dosing interval in accord with its long plasma half-life [58]. Ibuprofen, diclofenac, and nabumetone have less pronounced and/or less sustained antiplatelet effects. These clinical pharmacology data support the possibility that certain nonselective NSAIDs such as naproxen with both potent and sustained antiplatelet effects might provide aspirin-like protection from thrombotic cardiovascular events. Together, the clinical pharmacology data and the data from the OA studies suggest that in VIGOR, naproxen may have provided a cardioprotective effect. An analysis of thrombotic cardiovascular serious adverse experiences was also performed on data from placebo-controlled trials of rofecoxib in elderly patients with early Alzheimer's Disease. These data indicated that the incidence of thrombotic cardiovascular serious adverse experiences is similar in patients taking rofecoxib or placebo (Section 4.3.5) and are consistent with a lack of prothrombotic effect of rofecoxib, even in high risk elderly patients. These observations are supported by a meta-analysis of data from over 28,000 patients studied in Phase IIb to V rofecoxib clinical studies that included a placebo and/or a nonselective NSAID comparator. Together, the data are most consistent with a lowering of the risk of thrombotic cardiovascular events in VIGOR by naproxen and not an effect of rofecoxib to increase such risks.

The marketed experience with rofecoxib supports these conclusions. A review of the postmarketing experience with rofecoxib is provided in section 4.3.7. Based on a search of the Merck Worldwide Adverse Experiences Surveillance database on 13-Mar-2000, the reporting rate for thrombotic cardiovascular serious adverse experiences was 8.1 reports per 100,000 patient-treatment-years distributed. This rate is small relative to the background incidence of these events.

4.3.2 Overview of the Effects of Aspirin, Selective COX-2 Inhibitors, and Nonselective NSAIDs on Platelet Function

4.3.2.1 The Effects of Aspirin, Selective COX-2 Inhibitors, and Nonselective NSAIDs on Platelet Thromboxane Metabolism and Function

Cyclooxygenase and its prostanoid products have important roles in hemostasis. Prostacyclin (PGI_2), a product derived primarily through the activity of endothelial cell COX-1 and COX-2, is a vasodilator and inhibitor of platelet aggregation. Serum thromboxane A_2 (TXA_2), largely a product of platelet COX-1, is a vasoconstrictor and promotor of platelet aggregation. Aspirin, a well recognized antiplatelet agent and inhibitor of platelet TXA_2 synthesis, is effective in decreasing the risk of cardiovascular thrombotic events in patients at risk for such events. Aspirin's antiplatelet effect is mediated through its near complete, irreversible inhibition of platelet COX-1 activity. Even low-dose aspirin (≥81 mg/day) achieves nearly complete inhibition of platelet TXA_2 production. This effect on platelets is irreversible because these nonnucleated cells cannot replace the COX-1 enzyme that is permanently acetylated and inactivated by aspirin.

It is thought that, to serve as a vascular-protective agent, near-complete inhibition of TXA_2 synthesis sustained over time is needed [59]. The effect of chronic therapy with non-aspirin COX-1/COX-2 inhibitors (the nonselective NSAIDs) on the incidence of cardiovascular thrombotic events has not been well characterized. Although nonselective NSAIDs inhibit platelet COX-1 activity, this inhibition is reversible. Thus, the ability of a nonselective NSAID to provide potent and sustained antiplatelet effects that mimic aspirin's antiplatelet properties (and thus potentially to effect aspirin-like vascular-protection) is highly dependent on the unique COX-1/COX-2 potency and pharmacokinetic profiles of each of these compounds. In contrast to the nonselective NSAIDs or aspirin, COX-2 selective inhibitors such as celecoxib and rofecoxib do not have these platelet inhibitory effects because platelets do not express COX-2 [60].

Several studies have demonstrated that the nonselective COX-1/COX-2 inhibitors vary in the magnitude and time course of their effects on platelet function. These studies evaluated the effects of the NSAIDs on prostaglandin metabolism and platelet aggregation in normal subjects. TXA_2 and PGI_2 synthesis were monitored by measuring their stable metabolites, serum TXB_2 generated in clotted whole blood and urinary PGI-M (2,3-dinor $PGF_{1\alpha}$), respectively. As blood coagulates, platelets synthesize and release TXA_2. The synthesis of TXA_2 is dependent on COX-1. TXA_2 is converted spontaneously and non-enzymatically to TXB_2 which is measured. Prostacyclin (PGI_2) is synthesized systemically but is unstable and converted rapidly (and non-enzymatically) to 6-Keto-$PGF_{1\alpha}$ which itself undergoes metabolism to PGI-M. In addition to the measurement of these prostanoid metabolites, effects on platelet aggregation and bleeding time were studied. The MRL studies discussed in this section were presented in the original NDA for rofecoxib.

Studies reported in the original NDA explored the platelet effects of rofecoxib 12.5 to 50 mg. Protocol 063 investigated the effects of rofecoxib 50 mg daily on peak TXB_2 inhibition and on platelet aggregation. Therapy with rofecoxib 50 mg did not result in statistically significant inhibition of serum TXB_2 or platelet aggregation compared to placebo. Protocol 061 compared the effects of lower doses of rofecoxib and several nonselective COX-1/COX-2 inhibitors on thromboxane generation and platelet function [58]. Patients were randomized to receive 6 days of therapy with either placebo, rofecoxib 12.5 or 25 mg daily, diclofenac 50 mg 3 times daily, ibuprofen 800 mg 3 times daily, or naproxen 500 mg 2 times daily. The effects of therapy on COX-1 activity were assessed by measurement at steady state of the peak and time-weighted average inhibition (WAI) of TXB_2 generation. Time averaged inhibition of platelet aggregation was also determined. The use of time-averaged measurements allowed for determination of platelet effects across the entire dosing interval for each compound. As a point of reference for this study, 120 mg aspirin daily is reported to decrease TXB_2 generation by 94 ± 1% throughout the dosing interval [59]. Eighty-one (81) mg aspirin has similar effects [61]. In multiple studies in vivo, aspirin has been shown to significantly prolong bleeding time [62].

In Protocol 061, therapy with rofecoxib did not meaningfully inhibit platelet TXB_2 formation. Peak TXB_2 inhibition was similar among the nonselective NSAIDs. However, the nonselective NSAIDs differed in their effects when the entire dosing interval was taken into account. Therapy with diclofenac resulted in a 50% reduction in time-weighted average TXB_2 levels, ibuprofen in a 87% reduction in time-weighted average TXB_2 levels, and naproxen in a 95% reduction in time-weighted average TXB_2 levels (Figure 10). Similarly, platelet aggregation on Day 6 was not inhibited by therapy with rofecoxib or placebo. Therapy with naproxen resulted in substantial inhibition of platelet aggregation (88% mean time-averaged inhibition; SD = 1.9%) whereas therapy with diclofenac resulted in a modest 21% time-averaged inhibition of platelet aggregation (Figure 11).

Figure 10

Weighted Average Inhibition of TXB_2 WAI (%) by Different Nonselective NSAIDs or by the Selective COX-2 Inhibitor Rofecoxib (Mean ±SE)

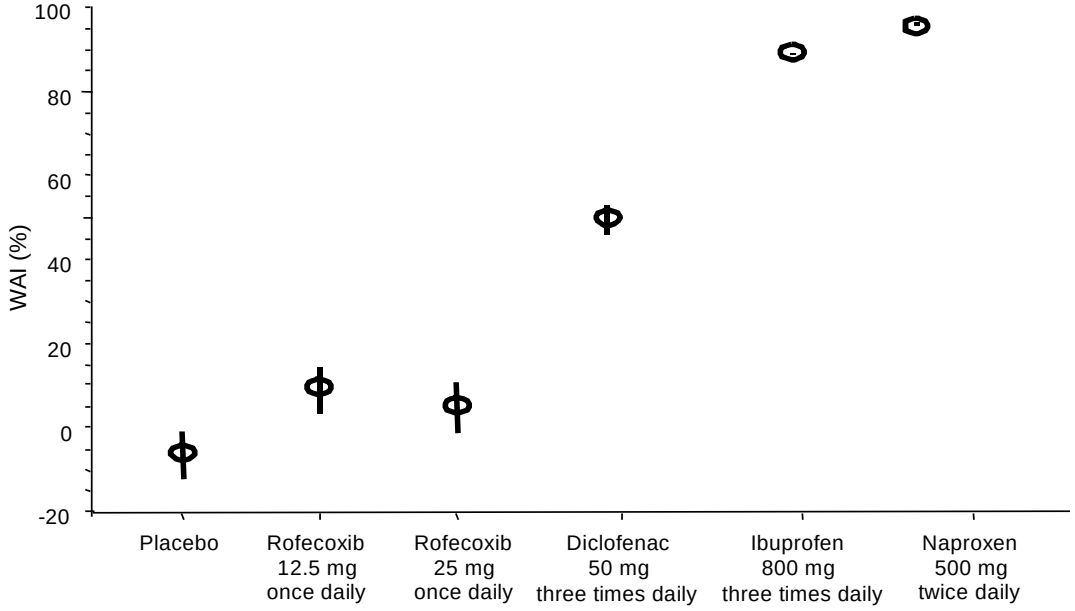
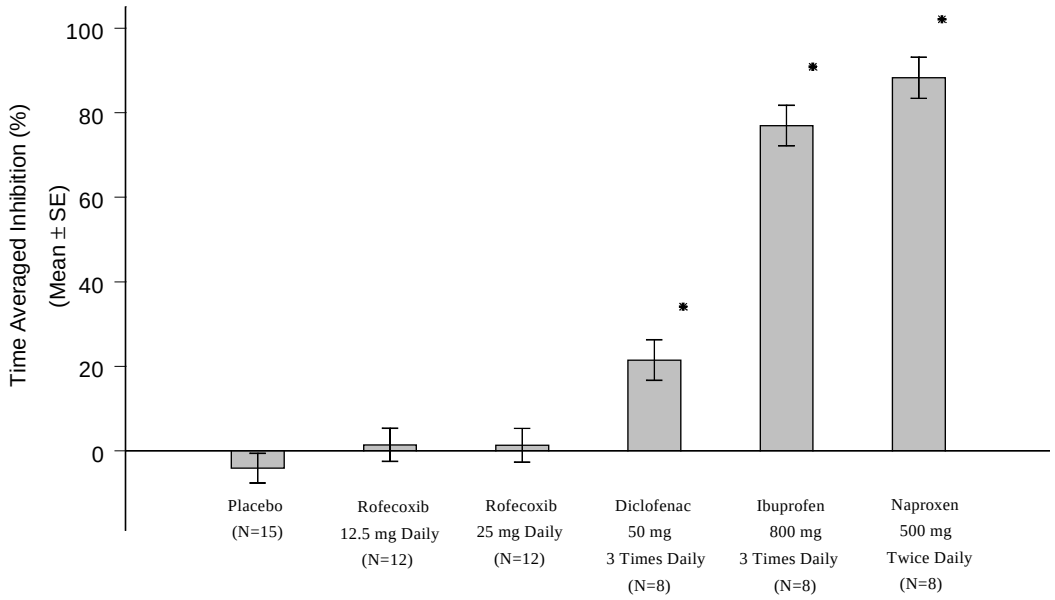


Figure 11

The Differential Effects of Nonselective COX-1/COX-2 Inhibitors and a COX-2 Selective Inhibitor on Ex Vivo Platelet Aggregation to 1 mM Arachidonic Acid

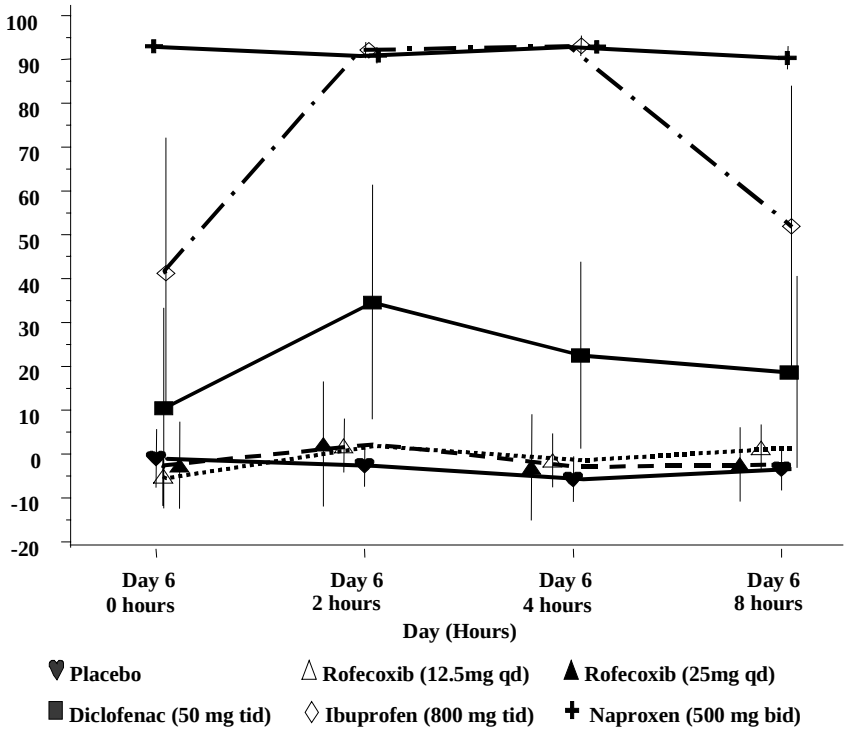


* p<0.001 versus placebo.

Inspection of the individual time points for the inhibition of TXB_2 and platelet aggregation from Protocol 061 further demonstrates the difference between these drugs (Figure 12). Note, in this figure, because drug effect was studied at steady state, the 0 hour time point is also the trough, i.e., 8 or 12 hours since the previous dose depending on the regimen. Only naproxen 500 mg twice daily (the top curve in the figure; symbol = ✚) showed ~90% inhibition of platelet aggregation consistently throughout its 12-hour dosing interval. The next most effective agent, ibuprofen 800 mg 3 times daily (the second curve; symbol = ♢), only provided maximal inhibition of platelet function at 2 and 4 hours after a dose and not at 8 hours (its trough time point). The maximal inhibition of platelet aggregation with diclofenac (third curve from the top; symbol = ■) was ~35% at 2 hours after dosing. At trough (12 hours after the prior dose), the mean inhibition of platelet aggregation by naproxen was 93.0% (range 89.7, 96.4%). In a separate study (Protocol 063), the mean inhibition of platelet aggregation by aspirin 81 mg daily at trough was 92.1% (range 84.1, 95.0). Thus, naproxen, but not ibuprofen or diclofenac, resulted in high-level inhibition of platelet aggregation throughout its dosing interval similar to that achieved by aspirin.

Figure 12

Percent Inhibition From Baseline Platelet Aggregation by
Time Point on Day 6 Using Arachidonic Acid as Agonist (Mean ±90% CI)



Consistent with these data, therapy with placebo, rofecoxib, and diclofenac did not result in a prolongation of bleeding time whereas therapy with naproxen prolonged bleeding time by ~79% [58]. This effect of naproxen on bleeding time is similar to the reported effect of aspirin (~50% prolongation) [63].

These studies thus demonstrated a gradient of antiplatelet effects among the NSAIDs. Therapy with naproxen was associated with antiplatelet effects similar to aspirin, diclofenac which does not provide sustained high level inhibition of platelet COX-1 resulted in modest antiplatelet effects, and rofecoxib was similar to placebo. The different effects of these drugs on hemostasis are reflected in their distinctive U.S. product labels [64 to 66].

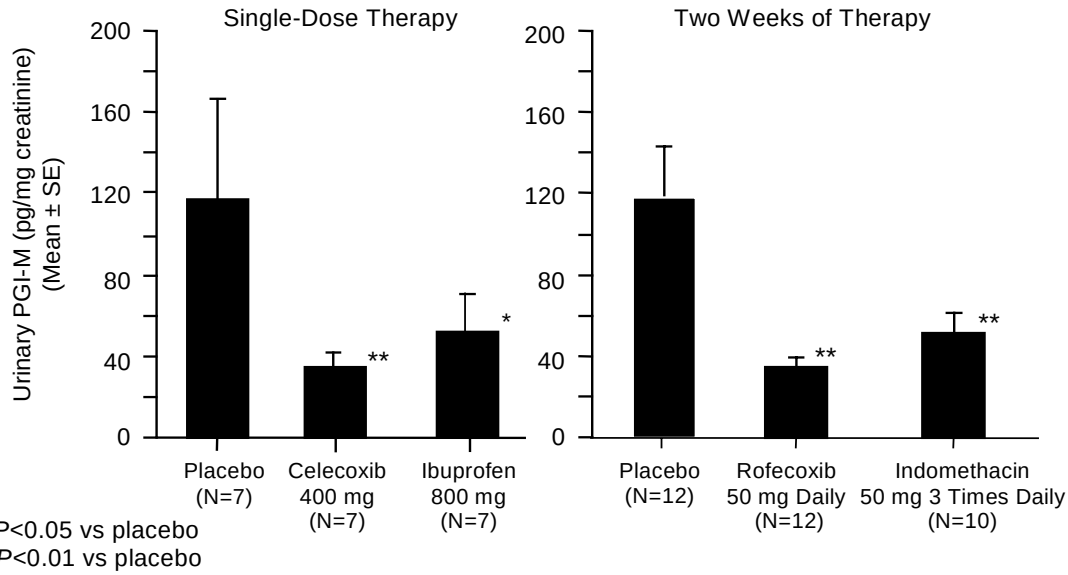
These results demonstrate that nonselective NSAIDs differ in their magnitude and/or duration of antiplatelet effects. They support the possibility that certain nonselective NSAIDs such as naproxen with both potent and sustained antiplatelet effects might provide aspirin-like protection from thrombotic cardiovascular events. Although naproxen has not been studied in this regard, other potent, reversible inhibitors of COX-1 have been studied. Flurbiprofen [67] 50 mg twice daily for 6 months was compared with placebo in the setting of coronary plaque rupture and reduced the incidence of recurrent myocardial infarction by 70% compared to placebo [68]. Indobufen [69] was shown to be similar to aspirin in preventing saphenous vein graft occlusion in patients undergoing cardiac bypass graft surgery [70] and significantly reduced, compared to placebo, thrombotic events in patients with atrial fibrillation or ischemic heart disease [71]. The data from these studies suggest that reversible nonselective COX-1/COX-2 inhibitors can demonstrate in clinical studies vascular-protective properties similar to those observed with aspirin.

4.3.2.2 The Effects of Selective COX-2 Inhibitors and of Nonselective NSAIDs on Prostacyclin Synthesis

The effects of nonselective NSAIDs and COX-2 selective inhibitors on systemic PGI_2 (prostacyclin) synthesis have also been studied. The effect of a single dose of celecoxib, ibuprofen, or placebo on this parameter was evaluated by FitzGerald et al. [72]. The effect of 14 days of therapy with rofecoxib 50 mg daily, indomethacin 50 mg 3 times daily, or placebo on this parameter was evaluated in Protocol 023 [73]. Results of these studies are shown in Figure 13. As measured by urinary PGI-M levels, PGI_2 synthesis was reduced ~45 to 70% for rofecoxib, indomethacin, ibuprofen, and celecoxib.

Figure 13

Systemic Prostacyclin Synthesis as Assessed by Urinary PGI-M Levels Following Therapy With COX-2 Selective Inhibitors and Nonselective NSAIDs



Data Source: [72; 73]

Both selective COX-2 inhibitors and nonselective NSAIDs inhibit the production of prostacyclin and do so to a similar extent. As previously alluded to, because prostacyclin is a vasodilator and an inhibitor of platelet aggregation, the theoretical possibility was suggested that therapy with COX-2 selective inhibitors, because they have no effect on platelet function yet lower prostacyclin synthesis, might result in proaggregatory effects. If this were true, patients taking selective COX-2 inhibitors might be expected to have an increased incidence of thrombotic events relative to placebo. As will be described later, while rofecoxib is devoid of effects on platelet function, it is not prothrombotic when compared to placebo.

4.3.2.3 Conclusions—Effects of Aspirin, Selective COX-2 Inhibitors, and Nonselective NSAIDs on Platelet Function

- Naproxen and aspirin are both potent inhibitors of platelet COX-1 with sustained effects across their dosing intervals on platelet TXB_2 generation and platelet aggregation.
- Naproxen and aspirin have similar effects on prolongation of bleeding time.

- The nonselective NSAIDs diclofenac and ibuprofen have either less potent or less sustained effects on platelet thromboxane synthesis and platelet aggregation than naproxen (or aspirin).
- The selective COX-2 inhibitors rofecoxib and celecoxib have no effects on platelet thromboxane synthesis and platelet aggregation, consistent with the observation that platelets do not express COX-2.
- Nonselective NSAIDs and selective COX-2 inhibitors inhibit the production of systemic prostacyclin to a similar degree.

These observations suggested the possibility that naproxen and other potent inhibitors of COX-1 with sustained effects across their dosing interval might provide aspirin-like protection from thrombotic cardiovascular events. They also raised a theoretical possibility that selective COX-2 inhibitors, because they inhibit prostacyclin production but not platelet function, might result in proaggregatory effects. To investigate these possibilities, in the second quarter 1998, MRL initiated a Cardiovascular Adjudication SOP to further evaluate whether there were any differences in the incidence of thrombotic cardiovascular serious adverse experiences during chronic therapy with rofecoxib versus nonselective NSAIDs or placebo.

4.3.3 The Adjudication Standard Operating Procedure (SOP)

As discussed above, a Cardiovascular Adjudication Standard Operating Procedure (Adjudication SOP) was developed for the post Phase III OA rofecoxib development program to obtain further data with regard to any difference in the incidence of thrombotic cardiovascular serious adverse experiences associated with chronic therapy with COX-2 selective inhibitors versus nonselective NSAIDs or placebo. The basis of the Adjudication SOP was a blinded systematic review by an expert panel of cardiologists, neurologists, and vascular medicine internists of events that, in the judgment of the site investigator, were thrombotic cardiovascular serious adverse experiences. These 3 separate Independent Adjudication Committees (one for cardiac events, one for cerebrovascular events, and one for peripheral vascular events) assigned potential thrombotic cardiovascular serious adverse experiences to one of the diagnostic categories established in the Adjudication SOP. A Vascular Events Coordination Center, staffed by MRL personnel, was responsible for the blinded surveillance for serious adverse experiences eligible for adjudication, assembly of adjudication packages, and for administration of the process. Adverse experience terms defining events that were eligible for adjudication are in Appendix 2.

4.3.4 Analysis of Thrombotic Cardiovascular Events—VIGOR Study

All available thrombotic cardiovascular event data from VIGOR are reported in this document. As described in the safety update report submitted to the FDA on 13-Oct-2000, the original cardiovascular events analysis included in a recent publication [74] and in the VIGOR sNDA (29-Jun-2000) did not include 11 patients in whom serious adverse experiences meeting criteria for adjudication were reported after 10-Feb-2000, the

termination date for the study selected by the Steering Committee. This date was prespecified as the cutoff date for events to be included in the primary cardiovascular analyses. However for completeness, events which were reported after this cutoff date were included in the subsequent safety update report of 13-Oct-2000. Five of these 11 patients had events confirmed by the Adjudication Committee as thrombotic serious adverse experiences. These events are included in this background document.

4.3.4.1 Cardiovascular Demographic Information in VIGOR

A total of 8076 patients were randomized. The mean age of the study cohort was 58.1 years and 79.7% were female. Approximately 6% of patients had a prior history of atherosclerotic cardiovascular disease, and half reported a cardiovascular risk factor (hypertension, diabetes mellitus, hypercholesterolemia, or smoking) other than one related to age or gender. The most common risk factor was hypertension. As discussed above, patients were not to use aspirin or other antiplatelet agents in VIGOR to prevent confounding of the primary GI analyses. Patients who were taking aspirin or other antiplatelet agents for vascular protection were to be excluded from enrollment in the study. Nevertheless, 4% of patients enrolled in the study met criteria for aspirin prophylaxis as outlined in the U.S. product circular for aspirin [64]. These patients accounted for nearly one third of the cardiovascular events (see Section 4.3.4.3).

4.3.4.2 Primary Analysis of Thrombotic Cardiovascular Serious Adverse Experiences in VIGOR

A total of 96 patients (64 in the rofecoxib group and 32 in the naproxen group) had 1 or more thrombotic serious adverse experiences which were referred to the adjudication committee (hereafter referred to as Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences). Of these, 64 patients had one or more events during VIGOR that were adjudicated as thrombotic events by the committees (hereafter referred to as Confirmed Thrombotic Cardiovascular Serious Adverse Experiences) (Table 15). In keeping with the data analysis section of the Adjudication SOP, Table 15 does not include 3 events that were determined by adjudication to be hemorrhagic cerebrovascular accidents. The overall incidence of confirmed thrombotic cardiovascular serious adverse experiences in VIGOR is presented by treatment group in Table 15. The rate of confirmed thrombotic cardiovascular serious adverse experiences was 0.70 per 100 patient-years for the naproxen group and 1.67 per 100 patient-years for the rofecoxib group. Thus, therapy with naproxen was associated with a 58% (95% CI: 28 to 75%) lower risk for the development of confirmed thrombotic cardiovascular serious adverse experiences, due primarily to a lower incidence of coronary events. Statistical analysis indicated that the lower risk for a confirmed thrombotic cardiovascular serious adverse experience observed with naproxen therapy was constant over time. An analysis of the investigator-reported thrombotic cardiovascular serious adverse experiences showed similar results; naproxen was associated with a 50% (95% CI: 24 to 67%) lower risk for the development of investigator-reported thrombotic cardiovascular serious adverse experiences.

Table 15

Analysis of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in VIGOR[†]

Event Category	Treatment Group	N	Patients With Events	PYR[‡]	Rates[‡]	Relative Risk[§] Estimate	95% CI
All thrombotic events	Rofecoxib	4047	45	2697	1.67		
	Naproxen	4029	19	2698	0.70	0.42	(0.25, 0.72)
All cardiac events	Rofecoxib	4047	28	2698	1.04		
	Naproxen	4029	10	2698	0.37	0.36	(0.17, 0.74)
All cerebrovascular events	Rofecoxib	4047	11	2699	0.41		
	Naproxen	4029	8	2699	0.30	0.73	(0.29, 1.80)
All peripheral vascular events	Rofecoxib	4047	6	2699	0.22		
	Naproxen	4029	1	2699	0.04	0.17	(0.00, 1.37)

[†] In keeping with the data analysis section of the Adjudication SOP, this table does not include events determined by adjudication to be hemorrhagic cerebrovascular accidents.
[‡] Per 100 patient-years at risk (PYR).
[§] Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.
Although a patient may have had 2 or more serious adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Table 16 presents the incidences of the various thrombotic cardiovascular serious adverse experience adjudication diagnoses. The incidence of cardiovascular death was low and not different between treatment groups. The incidence of confirmed acute myocardial infarction was 0.5% in patients treated with rofecoxib and 0.1% in patients treated with naproxen. Most of these events were judged to have occurred spontaneously (i.e., not as a consequence of a GI bleed, major surgery, or coronary revascularization).

Table 16

Summary of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in VIGOR

	Rofecoxib (N=4047)		Naproxen (N=4029)	
	n	(%)	n	(%)
Any Event†	**47**	**(1.2)**	**20**	**(0.5)**
Arterial Event†	42	(1.0)	19	(0.5)
Venous Event	5	(0.1)	1	(0.0)
Cardiovascular Death†	**6**	**(0.1)**	**6**	**(0.1)**
Fatal Acute Myocardial Infarction	2	(0.0)	0	(0.0)
Fatal Hemorrhagic Stroke	1	(0.0)	1	(0.0)
Fatal Ischemic Cerebrovascular Stroke	0	(0.0)	1	(0.0)
Sudden Cardiac Death	3	(0.1)	4	(0.1)
Cardiac Events (Fatal/Nonfatal)	**28**	**(0.7)**	**10**	**(0.2)**
Acute Myocardial Infarction	20	(0.5)	4	(0.1)
Sudden Cardiac Death	3	(0.1)	4	(0.1)
Unstable Angina Pectoris	5	(0.1)	3	(0.1)
Cerebrovascular Events (Fatal/Nonfatal)†	**13**	**(0.3)**	**9**	**(0.2)**
Hemorrhagic Stroke	2	(0.0)	1	(0.0)
Ischemic Cerebrovascular Stroke	9	(0.2)	8	(0.2)
Transient Ischemic Attack	2	(0.0)	0	(0.0)
Peripheral Vascular Events (Fatal/Nonfatal)	**6**	**(0.1)**	**1**	**(0.0)**
Peripheral Arterial Thrombosis	1	(0.0)	0	(0.0)
Peripheral Venous Thrombosis	5	(0.1)	1	(0.0)

† Includes patients who experienced a hemorrhagic stroke.
Patients may be counted in more than one row but are only counted once within a row.

4.3.4.3 Subgroup and Sensitivity Analyses of Thrombotic Cardiovascular Events in VIGOR

Thrombotic Cardiovascular Serious Adverse Experiences Analyzed by Baseline Risk Factors

The baseline demographics of the cohort of patients with confirmed thrombotic cardiovascular serious adverse experiences differ substantially from the overall population of patients in the study in that a greater percentage of patients with confirmed thrombotic cardiovascular serious adverse experiences had typical risk factors for atherosclerotic cardiovascular disease (Table 17). Compared with the overall VIGOR cohort, patients who experienced a confirmed thrombotic cardiovascular serious adverse experience were older (64% ≥65 years old for patients who experienced such an event versus 26% for the entire study) and more likely to be male (42% versus 20%) and/or current smokers (34% versus 19%). Patients with a confirmed thrombotic cardiovascular event had a substantially higher incidence of a history of atherosclerotic cardiovascular disease, hypertension, and hypercholesterolemia prior to enrollment than the general study population and 81% had at least 1 cardiovascular risk factor versus 50% for the entire study population.

Table 17

Baseline Cardiovascular Demographics of all Patients in VIGOR and Patients Who had a Confirmed Thrombotic Cardiovascular Serious Adverse Experience

Demographic	All Patients (N=8076)		Patients With Events (N=64)[†]	
	n	(%)	n	(%)
Age				
<65 Years Old	6009	(74.4)	23	(35.9)
≥65 Years Old	2067	(25.6)	41	(64.1)
Gender				
Female	6438	(79.7)	37	(57.8)
Male	1638	(20.3)	27	(42.2)
Past Cardiovascular History				
Past History of Atherosclerotic Cardiovascular Disease	454	(5.6)	21	(32.8)
Cardiovascular Risk Factors				
Any Cardiovascular Risk Factors	4035	(50.0)	52	(81.3)
Hypertension	2385	(29.5)	32	(50.0)
Diabetes Mellitus	494	(6.1)	3	(4.7)
Hypercholesterolemia	636	(7.9)	11	(17.2)
Current Smoker	1569	(19.4)	22	(34.4)
Indication for Aspirin Therapy				
Aspirin Therapy Indicated[‡]	321	(4.0)	18	(28.1)

[†] Two patients experienced >1 confirmed thrombotic cardiovascular serious adverse experience. AN 10677 (rofecoxib group) experienced 2 ischemic cerebrovascular accidents. AN 00560 (naproxen group) experienced unstable angina and myocardial infarction. Because the analysis of rates of confirmed thrombotic cardiovascular serious adverse experiences counted number of patients with events, these patients are counted once within each adjudication category.

[‡] Patients with past medical histories of one of the following cerebrovascular accident, transient ischemic attack, myocardial infarction, unstable angina, angina pectoris, coronary artery bypass graft surgery, or percutaneous coronary interventions.

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in Patients With a Baseline Indication for Vascular-Protective Aspirin Therapy

Patients with symptomatic coronary or cerebrovascular disease are at high risk for the development of recurrent thrombotic cardiovascular events. There is widespread agreement among cardiovascular public health authorities that chronic vascular-protective low-dose aspirin therapy is indicated in these patients for the prevention of recurrent thrombotic events. Of note, despite the proscription on the enrollment of patients in whom low-dose aspirin therapy was indicated, 4% of the patients in VIGOR met accepted criteria for aspirin therapy as outlined in the U.S. product circular for aspirin [64] (Table 17). The incidence of thrombotic cardiovascular serious adverse experiences occurred disproportionately in the population of patients in whom aspirin was indicated but who were not taking aspirin. In patients who received rofecoxib and had a confirmed thrombotic cardiovascular serious adverse experience, 33% had a past medical history of symptomatic coronary or cerebrovascular disease, and therefore a clear indication for chronic aspirin therapy. Although such patients accounted for only 4% of the study population, they experienced 28% of all confirmed thrombotic cardiovascular serious adverse experiences. These data highlight the benefit of adequate antiplatelet activity in such high-risk patients.

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in Patients Who Experienced Hypertension Adverse Experiences During the Study

A hypertension adverse experience occurred before the cardiovascular event in only 4 patients on rofecoxib (ANs 1449, 2044, 2214, and 7670). Thus only a minority of patients with a confirmed thrombotic cardiovascular serious adverse experience had developed a hypertension-related adverse experience prior to the event.

Two analyses were performed to determine if the imbalance in cardiovascular outcomes between the treatment groups in the study was related to whether or not a patient had a hypertension-related adverse experience prior to the cardiovascular event. The first analysis sought to determine if thrombotic cardiovascular serious adverse experiences were more common in patients who had an antecedent hypertension-related adverse experience (Table 18). The incidence rates of confirmed thrombotic serious adverse experiences were compared by treatment group in patients with and without an antecedent hypertension-related adverse experience. For the rofecoxib group, 1.0% of the patients who had an antecedent hypertension-related adverse experience had a thrombotic cardiovascular serious adverse experience whereas 1.1% of the patients had a thrombotic cardiovascular serious adverse experience without an antecedent hypertensive adverse experience; For naproxen, the 2 values are 0.0% and 0.5%, respectively.

Table 18

Incidence of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in Patients With and Without Hypertension-Related Adverse Experiences in VIGOR

Subgroup	Treatment Group	N	Patients With a Confirmed Cardiovascular Serious Adverse Experience	
			n	(%)
Incidence of a Confirmed Thrombotic Cardiovascular Serious Adverse Experience				
Patients with a hypertension-related adverse experience before the thrombotic event	Rofecoxib	394	4	(1.0)
Patients without a hypertension-related adverse experience before the thrombotic event	Rofecoxib	3653	41	(1.1)
Patients with a hypertension-related adverse experience before the thrombotic event	Naproxen	221	0	(0.0)
Patients without a hypertension-related adverse experience before the thrombotic event	Naproxen	3808	19	(0.5)

A second approach sought to determine if patients with confirmed thrombotic cardiovascular serious adverse experiences were more likely to have experienced an antecedent hypertension-related adverse experience (Table 19). Overall, only 4 of the 64 patients with confirmed thrombotic cardiovascular serious adverse experiences had also experienced an antecedent hypertension-related adverse experience. The incidence of hypertension-related adverse experiences occurring before a confirmed thrombotic cardiovascular serious adverse experience was comparable to the incidence of hypertension-related adverse experiences in patients without a confirmed thrombotic cardiovascular serious adverse experience.

Table 19

Incidence of Antecedent Hypertension-Related Adverse Experiences in Patients With and Without Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in VIGOR

Subgroup	Treatment Group	N	Patients With a Hypertension-Related Adverse Experience	
			n	(%)
Incidence of an Antecedent Hypertension-Related Adverse Experience				
Patients with a confirmed thrombotic cardiovascular serious adverse experience	Rofecoxib	45	4	(8.9)
Patients without a confirmed thrombotic cardiovascular serious adverse experience	Rofecoxib	4002	387	(9.7)
Patients with a confirmed thrombotic cardiovascular serious adverse experience	Naproxen	19	0	(0.0)
Patients without a confirmed thrombotic cardiovascular serious adverse experience	Naproxen	4010	220	(5.5)

Blood Pressure Measurements in Patients With and Without Confirmed Thrombotic Cardiovascular Serious Adverse Experiences

Changes in blood pressure measurements were compared in patients with and without confirmed thrombotic cardiovascular serious adverse experiences. As expected, in both treatment groups, mean systolic blood pressure in patients who had confirmed thrombotic events was 6 to 9 mm Hg higher at baseline compared to patients without events. However, mean changes from baseline in systolic and diastolic blood pressure were similar in rofecoxib-treated patients with and without confirmed thrombotic events. In addition, the percent of patients with elevations in blood pressure which exceeded 20 mm Hg in systolic blood pressure or 15 mm Hg in diastolic blood pressure was similar in patients with and without confirmed thrombotic events. Lastly, there was no correlation between the magnitude of change in blood pressure and the risk of sustaining a confirmed thrombotic event. Thus, differential effects on blood pressure do not appear to explain the imbalance in confirmed thrombotic cardiovascular serious adverse experiences in VIGOR.

4.3.4.4 Analysis of VIGOR Using the Antiplatelet Trialists' Collaboration Combined Endpoint

The most common and widely accepted method to quantify the overall cardiovascular impact of antithrombotic compounds in cardiovascular clinical trials is by determining the effect of these compounds on the incidence of fatal and irreversible morbid cardiovascular events [75; 76]. The metric used for such an analysis as defined by the Antiplatelet Trialists' Collaboration (APTC) is the incidence of the combined endpoint of cardiovascular, hemorrhagic, and unknown death, myocardial infarction, and cerebrovascular accident (APTC combined endpoint). An analysis of the APTC combined endpoint was performed for the VIGOR population (Table 20). Overall, the risk of the APTC combined endpoint was 49% lower (95% CI: 9 to 71%) in the naproxen group relative to the rofecoxib group in VIGOR. Of the individual endpoints, the incidence of death and stroke were the same in the 2 groups. The difference in the event rates between the treatment groups was due primarily to a difference in the rates of MI.

Table 20

Analyses of Confirmed Cardiovascular Events in VIGOR Using the Antiplatelet Trialists' Collaboration (APTC) Combined Endpoint

Event Category	Treatment Group	N	Number of Patients With Events	PYR[†]	Rates[‡]	Relative Risk[§] Estimate	95% CI
All Patients							
Cardiovascular deaths[‖], MI, stroke[¶]	Rofecoxib	4047	35	2698	1.30		
	Naproxen	4029	18	2698	0.67	0.51	(0.29, 0.91)
Cardiovascular deaths[‖]	Rofecoxib	4047	7	2700	0.26		
	Naproxen	4029	7	2699	0.26	1.00	(0.35, 2.85)
Myocardial infarction (MI)	Rofecoxib	4047	20	2699	0.74		
	Naproxen	4029	4	2699	0.15	0.20	(0.07, 0.58)
Stroke[¶]	Rofecoxib	4047	11	2699	0.41		
	Naproxen	4029	9	2699	0.33	0.82	(0.34, 1.97)

[†] Patient-years at risk.
[‡] Per 100 PYR.
[§] Relative risk of naproxen with respect to rofecoxib from unstratified Cox model where the number of cases is at least 11, otherwise relative risk is ratio of rates.
[‖] Includes sudden death, unknown cause of death, fatal myocardial infarction, fatal stroke (hemorrhagic or ischemic), fatal subarachnoid hemorrhage, fatal primary intracranial hemorrhage, fatal GI bleeding episode.
[¶] Includes fatal or nonfatal ischemic strokes, and fatal or nonfatal hemorrhagic strokes.

4.3.4.5 Additional Evidence for Antiplatelet Effects of Naproxen in VIGOR

Near-complete inhibition of platelet function is accompanied by a lower risk of an acute thrombotic cardiovascular event [75 to 78]. Therapy with compounds that confer this benefit such as aspirin also results in an increase in the incidence of minor bleeding events (mostly epistaxis, ecchymosis, and prolonged bleeding following minor trauma such as shaving) [64; 65; 79].

In VIGOR, naproxen was associated with a higher incidence of minor bleeding events relative to rofecoxib (2.7% versus 1.9%, difference = 0.8, 95% confidence interval of the difference = 0.1, 1.4). The largest differences between naproxen and rofecoxib occurred in those events typically associated with antiplatelet effects, such as ecchymosis and epistaxis. For the adverse experiences ecchymosis and epistaxis, naproxen therapy was associated with a 2.1- and 3.5-fold increased incidence relative to rofecoxib therapy, respectively. This analysis excluded bleeding events that occurred in the GI tract, as any increase in these events associated with naproxen therapy is confounded by the differences in GI toxicity associated with naproxen and rofecoxib. These results are consistent with the differences in antiplatelet properties observed between these 2 compounds in clinical pharmacology studies and independently provide support that naproxen has clinically important antiplatelet effects in vivo [58; 65; 72; 80].

4.3.4.6 Summary of Thrombotic Cardiovascular Serious Adverse Experiences in VIGOR

- In VIGOR, therapy with naproxen was associated with a lower incidence of confirmed thrombotic cardiovascular serious adverse experiences. Similar results were obtained in the analysis of investigator-reported thrombotic cardiovascular serious adverse experiences.
- The difference between the treatment groups in the rates of confirmed thrombotic cardiovascular serious adverse experiences in VIGOR was due primarily to a lower incidence of myocardial infarction in patients treated with naproxen.
- In the rofecoxib group, a substantial proportion (33%) of thrombotic cardiovascular serious adverse experiences occurred in the 4% of patients in whom vascular-protective antiplatelet therapy was clearly indicated but who had not received aspirin.
- In VIGOR, therapy with naproxen was also associated with an increased incidence of minor bleeding events typically associated with aspirin or other agents capable of sustained, potent inhibition of platelet function.
- The cardiovascular results of VIGOR taken by themselves cannot distinguish between an increased incidence of thrombotic cardiovascular serious adverse experiences on rofecoxib due to a prothrombotic effect or a decreased incidence on naproxen due to inhibition of platelet function.

4.3.5 Thrombotic Cardiovascular Serious Adverse Experiences in Other Rofecoxib Clinical Studies

To understand better the significance of the cardiovascular results of VIGOR, additional analyses were undertaken. The 2 largest sets of clinical trials data in terms of patient-years of exposure and numbers of events available for the cardiovascular analysis were the completed OA Phase IIb/III studies (1657 patient-years of active comparator-controlled exposure and 363 patient-years of placebo-controlled exposure for the rofecoxib group) and the ongoing studies in patients with early Alzheimer's Disease (Protocols 078 and 091) (1146 patient-years of placebo-controlled exposure for the rofecoxib group). The OA studies provide extensive experience with rofecoxib (doses ranging from 12.5 to 50 mg; average dose = 24.7 mg) in comparison to non-naproxen NSAIDs that do not have potent or sustained antiplatelet effects (i.e., ibuprofen, diclofenac, and nabumetone). The Alzheimer's Disease and Minimal Cognitive Impairment studies provide extensive experience with rofecoxib 25 mg in comparison to placebo in an elderly population at high risk for serious thrombotic cardiovascular events. This section will focus on these 2 sets of studies and on a predefined meta-analysis of data across all rofecoxib Phase IIb to V clinical studies that included placebo and/or nonselective NSAID comparators. In addition, an analysis of reports of thrombotic cardiovascular events in the postmarketing experience with rofecoxib will also be presented.

The analyses of thrombotic cardiovascular serious adverse experiences described in Sections 4.3.5.1 and 4.3.5.2 are based on the original, investigator-assigned diagnoses referred to as "Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences" and do not represent adjudicated data. The diagnoses provided by the site investigators were not confirmed by adjudication either because the studies predated the Adjudication SOP (Phase IIb/III osteoarthritis program) or because the studies are ongoing or recently completed and the adjudication results are incomplete. As noted in Section 4.3.4.2, in VIGOR, the analysis of investigator-reported thrombotic cardiovascular serious adverse experiences was similar to the analysis of confirmed thrombotic cardiovascular serious adverse experiences.

4.3.5.1 Osteoarthritis Phase IIb/III Studies: A Combined Analysis of Thrombotic Cardiovascular Serious Adverse Experience Rates in Rofecoxib Users Versus Diclofenac, Ibuprofen, or Nabumetone and Versus Placebo

As presented in the original NDA for rofecoxib, the OA safety database consists of 5435 osteoarthritis patients who participated in all 8 randomized, controlled Phases IIb/III clinical trials. The overall duration of exposure in active comparator-controlled periods was 1657 patient-years for the combined rofecoxib (all doses) group and 706 patient-years for the combined nonselective NSAID (all comparators) group. The overall duration of exposure in placebo-controlled periods was 363 patient-years for the combined rofecoxib (all doses) group and 127 patient-years for the placebo group. The mean age of patients was 63.0 years; approximately 73% of the patients were women.

More than 50% of patients had a preexisting history of 1 or more cardiovascular risk factors. Approximately 40% of patients had a history of hypertension. Thus, compared with VIGOR, the patients enrolled in these studies had OA, not RA, and had a slightly higher incidence of demographic features associated with an increased risk for cardiovascular morbidity and mortality.

Six of the OA protocols included a placebo comparator. The active comparators in the OA program were diclofenac 150 mg daily (69% of use) and ibuprofen 2400 mg daily (27%); nabumetone 1000 mg daily was used as a comparator in one 6-week study (Protocol 058) and accounted for only 30 patient-years of exposure (4% of use). These comparators do not provide sustained near maximal antiplatelet effects throughout their dosing interval (Section 4.3.2.1) [58; 81]. The average daily dose of rofecoxib was approximately 25 mg. As was the case for VIGOR, low-dose aspirin was not allowed in these trials (with the exception of Protocol 058, a single study comparing rofecoxib to placebo or nabumetone in elderly patients >80 years old with OA).

The incidence of investigator-reported thrombotic cardiovascular serious adverse experiences in these OA studies was similar between the rofecoxib and nonselective NSAID comparator treatment groups. The incidence of investigator-reported thrombotic cardiovascular serious adverse experiences was 2.05 per 100 patient-years (95% CI: 1.36, 2.74) in the rofecoxib treatment group compared with 2.27 per 100 patient-years (95% CI: 1.16, 3.38) in the combined nonselective NSAID group. In trials that compared rofecoxib with placebo, analysis of the placebo-controlled periods indicates that the incidence of investigator-reported thrombotic cardiovascular serious adverse experiences was 2.48 per 100 patient-years (95% CI: 0.86, 4.10) in the rofecoxib group compared with 2.36 per 100 patient-years (95% CI: 0.00, 5.04) in the placebo group. These placebo-controlled data should be viewed with caution due to the small numbers of patients, short exposure times involved (363 patient-years for the rofecoxib group and 127 patient-years for the placebo group), and wide confidence intervals. Summaries of the investigator-reported thrombotic cardiovascular serious adverse experience categories in the various treatment groups are in Table 21 and Table 22. There are no individual thrombotic events whose rates suggest an imbalance between the groups.

Table 21

Summary of Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences Comparison of Rofecoxib With Nonselective NSAIDs Phase IIb/III Clinical Program for Rofecoxib in Osteoarthritis Patients

	Rofecoxib (N=3357)†		Nonselective NSAIDs (N=1564)‡	
	n	(%)	n	(%)
Patients with one or more investigator-reported thrombotic cardiovascular serious adverse experiences	34	(1.0)	16	(1.0)
Coronary Artery Disease Terms				
Cardiac Arrest	0	(0.0)	2	(0.1)
Acute Myocardial Infarction	3	(0.1)	0	(0.0)
Myocardial Infarction	5	(0.1)	3	(0.2)
Coronary Artery Occlusion	1	(0.0)	1	(0.1)
Unstable Angina	2	(0.1)	0	(0.0)
Angina Pectoris	2	(0.1)	4	(0.3)
Coronary Vasospasm	1	(0.0)	0	(0.0)
Coronary Artery Disease	4	(0.1)	2	(0.1)
Cerebrovascular Disease Terms				
Cerebrovascular Accident	6	(0.2)	3	(0.2)
Transient Ischemic Attack	3	(0.1)	0	(0.0)
Peripheral and Other Vascular Disease Terms				
Arterial Occlusion	1	(0.0)	0	(0.0)
Deep Venous Thrombosis	4	(0.1)	0	(0.0)
Peripheral Vascular Disorder	1	(0.0)	0	(0.0)
Pulmonary Embolism	1	(0.0)	0	(0.0)
Vascular Insufficiency	0	(0.0)	1	(0.1)

† These patients represent 1657 patient-years at risk.
‡ These patients represent 706 patient-years at risk.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Table 22

Summary of Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences, Comparison of Rofecoxib With Placebo
Phase IIb/III Clinical Program for Rofecoxib in Osteoarthritis Patients

	Rofecoxib (N=1701)†		Placebo (N=514)‡	
	n	(%)	n	(%)
Patients with one or more investigator-reported thrombotic cardiovascular serious adverse experiences	9	(0.5)	3	(0.6)
Coronary Artery Disease Terms				
Acute Myocardial Infarction	0	(0.0)	1	(0.2)
Myocardial Infarction	1	(0.1)	0	(0.0)
Unstable Angina	1	(0.1)	1	(0.2)
Coronary Artery Disease	2	(0.1)	0	(0.0)
Cerebrovascular Disease Terms				
Cerebrovascular Accident	3	(0.2)	1	(0.2)
Transient Ischemic Attack	1	(0.1)	0	(0.0)
Peripheral and Other Vascular Disease Terms				
Pulmonary Embolism	1	(0.1)	0	(0.0)

† These patients represent 363 patient-years at risk.
‡ These patients represent 127 patient-years at risk.
Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

A comparison of the incidence rates and 95% confidence intervals for investigator-reported serious thrombotic events in the VIGOR and active-comparator controlled OA Phase IIb/III studies is presented in Table 23. Some caution needs to be observed in comparing the point estimates of these rates. Because the studies were neither designed nor powered for this type of analysis, the confidence intervals between several of the groups are overlapping. In addition, cardiovascular risk factors differ between the studies. The patients in VIGOR were on average approximately 5 years younger than the OA patients and more were female. However, all the patients in VIGOR had RA and cardiovascular mortality is increased in RA patients even after adjusting for age and gender [82 to 84].

Table 23

Incidence of Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences, Comparison of Rofecoxib With Nonselective NSAIDs Phase IIb/III Clinical Program for Rofecoxib in Osteoarthritis Patients and VIGOR in Rheumatoid Arthritis Patients

Study	Treatment Group	N	Patients With Events	PYR[†]	Rate[‡]	95% CI of Rate
OA Phase IIb/III	Rofecoxib 25 mg	3357	34	1657	2.05	(1.36, 2.74)
	Nonselective NSAIDs	1564	16	706	2.27	(1.16, 3.38)
VIGOR	Rofecoxib 50 mg	4047	64	2695	2.37	(1.79, 2.96)
	Naproxen 1000 mg	4029	32	2696	1.19	(0.78, 1.60)

[†] Patient-years at risk.
[‡] Per 100 PYR.

Despite these caveats, it is of interest that the point estimates of the incidence rates for investigator-reported thrombotic cardiovascular serious adverse experiences in the Phase IIb/III osteoarthritis studies (2.05 events/100 patient-years at risk for the rofecoxib cohort, 2.27 events/100 patient-years at risk for the comparator NSAID cohort) were similar to the incidence rate for investigator-reported thrombotic cardiovascular serious adverse experiences in the rofecoxib arm in VIGOR (2.37 events/100 patient-years at risk). In contrast, the point estimate of the incidence rate of investigator-reported events in the naproxen arm of VIGOR was about half (1.19 events/100 patient-years at risk). Thus, in evaluating the OA trials and VIGOR in aggregate, the outlier appears to be the investigator-reported thrombotic cardiovascular serious adverse experience event rate in the naproxen arm of VIGOR, which was substantially lower than the event rates observed in the various treatment arms of the OA Phase IIb/III database or the rofecoxib arm of VIGOR.

It is also of interest that nearly identical rates of investigator-reported thrombotic cardiovascular serious adverse experiences were observed in OA patients taking an average dose of rofecoxib 25 mg daily in the Phase IIb/III OA program and in RA patients taking rofecoxib 50 mg daily in VIGOR. Thus, there is no evidence for a dose-response relationship between rofecoxib and investigator-reported thrombotic cardiovascular serious adverse experiences; such a relationship might be expected if rofecoxib were prothrombotic.

4.3.5.2 Thrombotic Cardiovascular Serious Adverse Experiences in Rofecoxib Users Versus Placebo in the Early Alzheimer's Disease Clinical Program for Rofecoxib

Additional experience with rofecoxib use compared with placebo is available from 2 large placebo-controlled trials in elderly patients with early Alzheimer's disease (Protocols 078 and 091). Although still ongoing, on 15-Sep-2000, cardiovascular serious adverse experiences were unblinded by an MRL statistician and statistical programmer involved in the VIGOR project. These personnel have no involvement with either oversight or analysis of these studies. Because these studies are ongoing, all data presented for these trials should be viewed as preliminary.

Protocol 078 (The Safety and Efficacy of Rofecoxib for the Prevention of Alzheimer's Disease in Patients at Risk) is a placebo-controlled, parallel-group, double-blind study in 1406 patients to evaluate the effects of rofecoxib 25 mg daily on the prevention of Alzheimer's disease and cognitive decline in patients ≥65 years of age with mild cognitive impairment. Protocol 091 (The Safety and Efficacy of Rofecoxib in Slowing the Progression of the Symptoms of Alzheimer's Disease) is a placebo-controlled, parallel-group, 15-month, double-blind study in 682 patients to evaluate the efficacy and safety of rofecoxib 25 mg to slow the progression of symptoms of Alzheimer's disease. As of 15-Sep-2000, more than 2090 patients have been randomized. At the time of analysis, the total duration of exposure in each treatment group was approximately 1200 patient-years.

Patients who were taking aspirin or other antiplatelet agents for cardiovascular protection, and patients in whom aspirin or other antiplatelet agents were indicated for cardiovascular-protective effect in the opinion of the study investigator, were to be excluded from enrollment in both of these studies. However, because these patients are elderly and may be at risk for atherosclerotic cardiovascular disease complications, therapy with aspirin or clopidogrel has been allowed if, during the study period, the investigator determined that it was indicated. A sensitivity analysis that excluded patients who had used aspirin or clopidogrel prior to study start was performed as part of the meta-analysis (Section 4.3.5.4).

The patients in these studies are mostly elderly (95% ≥65 years old). Men accounted for 61% of the patients. In addition to age, one or more risk factors for cardiovascular disease (history of hypertension, smoking, diabetes, or hypercholesterolemia) was present in 55% of the patients and 15% of all patients had a prior history of symptomatic atherosclerotic cardiovascular disease. Thus, compared with the patients in VIGOR or in all OA Phase IIb/III studies, this population of patients was older and at a relatively higher risk for serious thrombotic cardiovascular events.

The incidence of investigator-reported thrombotic cardiovascular serious adverse experiences is presented for the 2 studies combined (Table 24). Investigator-reported thrombotic cardiovascular serious adverse experiences and the subgroup of terms constituting myocardial infarction are similar between the 2 treatment groups. The rates

of investigator-reported thrombotic cardiovascular serious adverse experiences per 100-patient years were 2.81 for the rofecoxib group and 3.31 for the placebo group. The relative risk of having an event in the rofecoxib versus placebo groups was 0.85 (95% CI: 0.53, 1.35). That is, the risk was lower in the rofecoxib group.

The incidence of cardiac events were similar between the 2 groups. There were 9 MI-related serious adverse experiences (acute MI, MI, non-Q-Wave MI) in the rofecoxib group and 12 in the placebo group. There were 9 cerebrovascular events in the rofecoxib group and 19 in the placebo group.

Table 24

Pooled Summary of Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences in Protocols 078 and 091 in Patients With Mild Cognitive Impairment or Early Alzheimer's Disease

Endpoint Term	Rofecoxib (N=1041)[†]		Placebo (N=1050)[‡]	
	n	(%)	n	(%)
Total Number of Patients With Thrombotic Cardiovascular Serious Adverse Experiences	**32**	**(3.1)**	**40**	**(3.8)**
Cardiac Events	**21**	**(2.0)**	**19**	**(1.8)**
Acute Myocardial Infarction	2	(0.2)	3	(0.3)
Angina Pectoris	1	(0.1)	4	(0.4)
Cardiac Arrest	1	(0.1)	0	(0.0)
Coronary Artery Disease	7	(0.7)	3	(0.3)
Coronary Artery Stenosis	1	(0.1)	1	(0.1)
Myocardial Infarction	7	(0.7)	8	(0.8)
Non-Q-Wave Myocardial Infarction	0	(0.0)	1	(0.1)
Unstable Angina	1	(0.1)	2	(0.2)
Ventricular Fibrillation	1	(0.1)	0	(0.0)
Ventricular Tachycardia	0	(0.0)	2	(0.2)
Cerebrovascular Events	**9**	**(0.9)**	**19**	**(1.8)**
Carotid Artery Obstruction	1	(0.1)	7	(0.7)
Cerebrovascular Accident	2	(0.2)	5	(0.5)
Lacunar Infarction	0	(0.0)	1	(0.1)
Transient Ischemic Attack	6	(0.6)	6	(0.6)

Table 24 (Cont.)

Pooled Summary of Investigator-Reported Thrombotic Cardiovascular Serious Adverse Experiences in Protocols 078 and 091 in Patients With Mild Cognitive Impairment or Early Alzheimer's Disease

Endpoint Term	Rofecoxib (N=1041)†		Placebo (N=1050)‡	
	n	(%)	n	(%)
Other Events	**2**	**(0.2)**	**3**	**(0.3)**
Deep Venous Thrombosis	0	(0.0)	1	(0.1)
Femoral Artery Occlusion	0	(0.0)	1	(0.1)
Intracranial Hemorrhage	0	(0.0)	1	(0.1)
Pulmonary Embolism	1	(0.1)	0	(0.0)
Thrombosis	1	(0.1)	0	(0.0)
Vascular Graft Occlusion	0	(0.0)	1	(0.1)

† These patients represent 1146 patient-years at risk.
‡ These patients represent 1221 patient-years at risk.
Note: Patients may be counted in more than one row but are only counted once within a row.

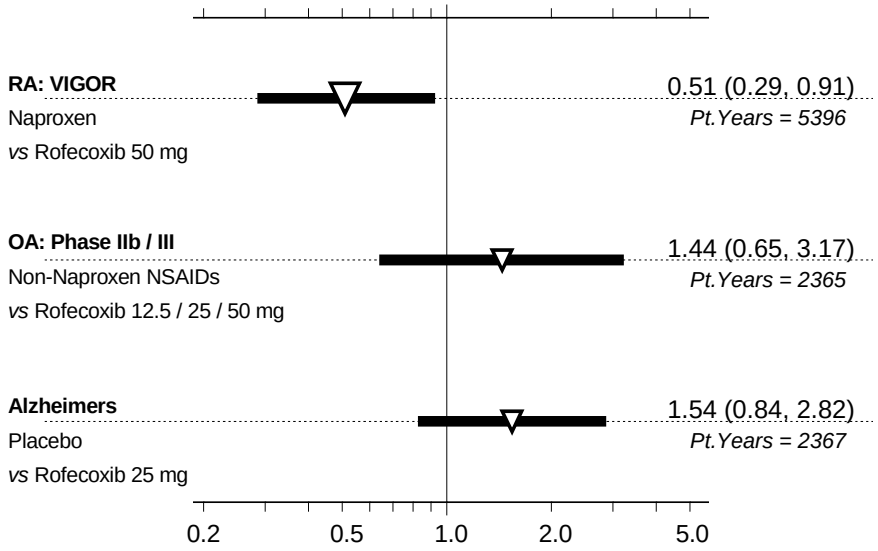
4.3.5.3 Comparison of Cardiovascular Events in the Clinical Trials Program for Rofecoxib in VIGOR, Osteoarthritis, and Early Alzheimer's Disease Using the APTC Combined Endpoint

To further analyze and compare the risk of thrombotic cardiovascular events in patients taking other therapies relative to rofecoxib, the relative risk of the APTC combined endpoint (cardiovascular and unknown death, MI, or cerebrovascular accident) along with the 95% CI was plotted for the VIGOR, Phase IIb/III OA, and Alzheimer Disease studies (Figure 14). In this figure, the area of the triangle is proportional to the number of patient-years accounted for; the triangle points to the relative risk estimate and the horizontal bars represent the 95% confidence intervals. Statistical significance of a result can be inferred if the 95% confidence interval for relative risk does not include 1.0.

This analysis of the APTC combined endpoint in Figure 14 is consistent with the "investigator-reported serious thrombotic cardiovascular events" analyses above. Thus, in placebo-controlled studies of patients with Alzheimer's Disease, and in studies comparing nonselective NSAIDs (other than naproxen) to rofecoxib, the risk of these cardiovascular events is similar in patients taking rofecoxib or patients taking comparator. The only statistically significant difference in risk between a comparator group and rofecoxib occurred in VIGOR in which the comparator was naproxen.

Figure 14

Comparisons of Relative Risk and 95% CI of the Antiplatelet Trialists' Collaboration (APTC) Combined Endpoint for Naproxen (VIGOR Study), Non-naproxen NSAIDs (OA Phase IIb/III Studies) and Placebo (Alzheimer's Disease Studies) Versus Rofecoxib



4.3.5.4 Meta-Analysis of the Risk of Thrombotic Cardiovascular Events in Rofecoxib or Nonselective NSAID Users Across All Rofecoxib Clinical Trials Using the Antiplatelet Trialists' Collaboration (APTC) Combined Endpoint

In addition to the clinical studies described above, the rofecoxib clinical program has included several smaller studies in diverse patient populations. To provide a global assessment of cardiovascular outcomes in the rofecoxib clinical program to date, a meta-analysis of all relevant ongoing and completed studies of rofecoxib was performed. The focus of the meta-analysis was to provide a more complete picture of the relative risk of sustaining a thrombotic event in patients taking placebo and nonselective NSAIDs as compared to rofecoxib, to improve precision in the estimate of relative risks for the development of a cardiovascular serious adverse experience between rofecoxib and naproxen, rofecoxib and placebo, and rofecoxib and non-naproxen nonselective NSAIDs,

and to determine if the conclusions from the individual studies described above (VIGOR, OA Phase IIb/III, Alzheimer's Disease) would be either altered or strengthened by inclusion of all relevant data.

Studies were included in the meta-analysis if they were a Phase IIb through Phase V study, were at least 4 weeks long, and included either placebo and/or active-comparator nonselective NSAID controls. Studies in which rofecoxib was compared with celecoxib or that were conducted in healthy volunteers were excluded. The celecoxib studies were excluded because they did not provide data to address the questions being asked; that is, comparisons to nonselective NSAIDs and placebo. Studies in healthy volunteers were excluded because of the substantially different patient population (e.g., differences in underlying cardiovascular risk factors, etc.)

The meta-analysis is a prespecified ongoing project; the results will be periodically updated as additional sets of data become unblinded. The studies included in this initial meta-analysis were all trials completed and unblinded in early Sep-2000, as well as 2 ongoing trials in Alzheimer's Disease/Minimal Cognitive Impairment patients. Interim data from the 2 Alzheimer's studies were included using a cutoff of 15-Sep-2000. A description of clinical studies that were included in the analysis is in Table 25.

Table 25

Studies Included in Meta-Analysis

Indication for Therapy	Protocol No.	Short Study Title	Total Sample Size	Planned Duration	Rofecoxib Doses (mg)	NSAID Comparator	Placebo Group	Aspirin Allowed at Study Start
Rheumatoid	068	Phase IIb dose finding	634	2 years	25/50	Naproxen	✓	
Arthritis	096	Phase III pivotal U.S.	909	1 year	12.5/25/50	Naproxen	✓	✓
	097	Phase III pivotal Intl.	1058	1 year	25/50	Naproxen	✓	
	098 + 103	Phase III endoscopy	660	13 weeks	50	Naproxen	✓	
	088 + 089	VIGOR	8076	9 months†	50	Naproxen		
Osteoarthritis	069‡	Phase IIb/III OA filing studies	5505	≤ 86 weeks	12.5/25/50	Other§	✓	
	083	Bone metabolism study	305	15 months	25	Other‖	✓	
	085	Nabumetone Study #1	1042	6 weeks	12.5	Other¶	✓	✓
	090	Nabumetone Study #2	978	6 weeks	12.5	Other¶	✓	✓
	901	Naproxen study	481	6 weeks	12.5	Naproxen		✓
	902	Arthrotec study	483	6 weeks	12.5	Other#		
	102 + 903	ADVANTAGE	5556	12 weeks	25	Naproxen		✓
Other	078	Alzheimer's prevention	1406	4 years††	25	--	✓	
	091	Alzheimer's treatment	682	15 months‡‡	25	--	✓	
	120	Phase III chronic low back pain	380	4 weeks	25/50	--	✓	✓
	121	Phase III chronic low back pain	310	4 weeks	25/50	--	✓	✓

† Duration was event based, median duration reported, maximum duration was 13 months.
‡ 069 refers to the set of 8 Phase IIb/III studies referenced in Protocol 069: 029, 033, 034, 035, 040, 044, 045, 058.
§ Diclofenac, ibuprofen and nabumetone.
‖ Ibuprofen.
¶ Nabumetone.
# Diclofenac.
†† Interim look at approximately 28 months after first patient enrolled in study.
‡‡ Interim look at approximately 12 months after first patient enrolled in study.

The primary objective of this analysis was to estimate the incidence rates of the APTC combined endpoint in patients treated with nonselective NSAIDs (naproxen, and other nonselective NSAIDs examined separately) or placebo compared to those treated with rofecoxib. A sensitivity analysis comparing the rates between the combined NSAIDs and placebo groups and the rofecoxib group was carried out to maximize power. The comparisons of interest were:

- Any NSAID/placebo versus rofecoxib.
- Naproxen versus rofecoxib.
- Other (non-naproxen) NSAIDs versus rofecoxib.
- Placebo versus rofecoxib.
- Other (non-naproxen) NSAIDs/placebo versus rofecoxib.

All analyses were conducted according to the same modified intention-to-treat principle used in VIGOR. Patients were included in the treatment group to which they were randomized, and only patients who received at least one dose of study drug were included in the analysis. The duration of follow-up for adverse experiences was 14 days after time of study discontinuation.

The previous analyses had suggested that naproxen might be cardioprotective and different from other NSAIDs or placebo. However, to maximize the ability of the meta-analysis to detect a difference between rofecoxib and placebo or nonselective NSAIDs, the most conservative approach was to consider that no NSAIDs are cardioprotective and to consider nonselective NSAIDs and placebo as a single group. Thus, the first analysis was to compare rofecoxib to all comparators and ask if there was any evidence for a difference in risk in the 2 groups.

Over 28,000 patients have been treated with either rofecoxib or nonselective NSAID/placebo in Phase IIb to V clinical studies (Table 26). This represents over 14,000 patient-years at risk. The rates of the APTC combined endpoint were 1.24 per 100 patient-years in the rofecoxib group and 1.16 per 100 patient-years in the combined nonselective NSAIDs/placebo group. The relative risk of an event was 0.91 for the combined group versus rofecoxib (95% CI: 0.67, 1.24) Thus, when all clinical studies are evaluated together, there is no evidence for a difference in the risk of an event in rofecoxib users versus any comparator nonselective NSAID or placebo.

However, an important factor to consider in a meta-analysis is whether the constituent studies can be combined. In general, the results of individual studies or groups of studies must not be obviously disparate if they are to be combined. The statistical test for homogeneity is used to determine if the relative risks are similar within treatment categories (e.g. NSAID/placebo; rofecoxib). For these rofecoxib studies, there was significant heterogeneity. Because of this heterogeneity, it is important to look at the individual studies to determine where the difference(s) lie. This was done by comparing groups of studies based on the comparator used: naproxen, non-naproxen nonselective NSAID, or placebo.

The relative risk of the APTC combined endpoint in naproxen users versus rofecoxib users was 0.59 (95% CI: 0.37, 0.94) (Table 26) consistent with the results observed in VIGOR and with a decreased incidence of the APTC endpoint in the naproxen group. Statistical significance of this result is demonstrated by the fact that the 95% confidence interval does not cross 1.00. In the other comparisons, the incidence of the APTC endpoint was decreased in the rofecoxib group. The relative risk of the APTC combined endpoint in non-naproxen nonselective NSAID users versus rofecoxib was 1.27 (95% CI: 0.64, 2.50) (Table 26). The relative risk in placebo versus rofecoxib users was 1.19 (95% CI: 0.73, 1.96) (Table 26). Analysis across groups of studies demonstrates that there was a borderline significant difference (p=0.057) between the relative risk of rofecoxib compared to naproxen and rofecoxib compared to other nonselective NSAIDs. This result implies that the relative risk of 0.59 seen in the comparison to naproxen tended to be different than the relative risk of 1.27 seen in the comparison to other NSAIDs and suggests a difference between naproxen and nonselective NSAIDs with regard to the risk of these events.

Table 26

Meta-Analysis of APTC Combined Endpoint, Rofecoxib Versus Comparator Agents

Comparison	Rofecoxib		Comparator		Relative risk (95% CI)[§]
	N	Cases/PYR[†] (Rate[‡])	N	Cases/PYR[†] (Rate[‡])	
Any nonselective NSAID or placebo versus rofecoxib	15136	96/7758 (1.24)	13213	73/6316 (1.16)	0.91 (0.67, 1.24)[‖]
Naproxen versus rofecoxib	9083	57/4622 (1.23)	7870	27/3742 (0.72)	0.59 (0.37, 0.94)
Non-naproxen NSAIDs versus rofecoxib	4549	21/1934 (1.09)	2755	14/984 (1.42)	1.27 (0.64, 2.50)
Placebo versus rofecoxib	6290	33/2189 (1.51)	3482	32/1678 (1.91)	1.19 (0.73, 1.96)
Non-naproxen NSAIDs or placebo versus rofecoxib	7675	42/3472 (1.21)	6017	46/2648 (1.74)	1.31 (0.86, 2.01)

[†] Patient-years at risk.
[‡] Per 100 PYR.
[§] Relative risk of comparator with respect to rofecoxib from Cox model stratified by indication.
[‖] This estimate is provided for information only since it represents pooling of heterogenous cohorts.

Although the studies examining rofecoxib and naproxen were different from the others with regard to relative risk of events, the studies comparing rofecoxib and placebo or rofecoxib and non-naproxen nonselective NSAIDs were not different. Therefore, it would be valid to combine the results from studies in which the comparator was either a non-naproxen nonselective NSAID or placebo. Doing this would provide the most power and precision to identify any difference between rofecoxib and non-naproxen comparators. This analysis was performed and is shown in the last line of Table 26. In over 13,000 patients studied and over 6000 patient-years at risk, the overall incidence of the APTC combined endpoint was numerically higher in the "nonselective NSAIDs (other than naproxen) or placebo" group versus rofecoxib group. The relative risk of the APTC combined endpoint in the "nonselective NSAIDs (other than naproxen) or placebo" group versus rofecoxib was 1.31 (95% CI: 0.86, 2.01) (Table 26). Thus, there is no evidence of a difference in the risk of events for rofecoxib in comparison to non-naproxen NSAIDs or placebo.

Some of the studies included in the analysis allowed the use of aspirin/clopidogrel during the study (Table 25). Although the number of patient years for "aspirin users" was low, because of the potential for aspirin use to confound the results of the analysis, a subgroup analysis was conducted only in patients who were not taking aspirin/clopidogrel prior to study start. This subgroup analysis, which included >88% of the events, provided consistent results with the primary approach.

4.3.5.5 Summary—Cardiovascular Events in the Clinical Trials Program for Rofecoxib

The aggregate of the data from the OA clinical program, from placebo controlled studies in patients with cognitive impairment and/or Alzheimer's Disease, and from a meta-analysis combining all relevant rofecoxib studies indicate that rofecoxib use is associated with similar rates of cardiovascular thrombotic events as either placebo or most nonselective NSAIDs. These data are consistent with a lack of prothrombotic effects of rofecoxib. However, in naproxen-treated patients, there is a reduced incidence of serious thrombotic cardiovascular events compared to all of the other groups (rofecoxib, placebo, or other nonselective NSAIDs). Data from clinical pharmacology studies demonstrate that nonselective NSAIDs vary in their ability to inhibit platelet thromboxane production and platelet aggregation largely as a result of differences in intrinsic potency and pharmacokinetics. Naproxen, however, achieves 95% inhibition of platelet thromboxane synthesis as measured throughout the dosing interval. Thus, mechanistically, naproxen has antiplatelet effects similar to what is reported for aspirin. Consistent with its antiplatelet effect, patients taking naproxen in VIGOR as compared with patients taking rofecoxib had significantly more adverse experiences of epistaxis and ecchymosis, bleeding events typical of patients on antiplatelet therapy. Thus, the imbalance in the rates of cardiovascular thrombotic events between rofecoxib and naproxen groups in VIGOR is most consistent with the interpretation that naproxen, by virtue of its potent and sustained antiplatelet effects, afforded protection to patients at risk for these events.

The observation of a cardioprotective effect of naproxen in VIGOR may have been influenced by several protocol design factors. First, there was a high rate of compliance with study therapy in VIGOR, in part because patients were frequently reminded by telephone to take study medicine and were encouraged to comply at study visits when pill counts were performed. Thus, patients taking naproxen were unlikely to experience periods in which antiplatelet effects were absent. Although naproxen's antiplatelet effects are maintained throughout the dosing interval, naproxen is a reversible inhibitor of platelet COX-1. Naproxen's antiplatelet effects would be expected to wane if therapy is interrupted.

Second, VIGOR was conducted exclusively in RA patients. Cardiovascular mortality is increased in patients with RA [82-84]. Although markers for increased risk of cardiovascular disease are qualitatively similar in patients with and without RA, the frequency of finding elevated markers such as C-reactive protein [85 to 88] or anticardiolipin antibodies [89 to 94] may be higher in patients with RA. In this regard, RA patients represent a relatively high-risk population for cardiovascular thrombotic events. The ability to demonstrate a cardioprotective effect of antiplatelet agents is facilitated by the study of high-risk populations [75; 76]. Importantly, in another high risk population, the elderly with early Alzheimer's Disease, the incidence of thrombotic cardiovascular serious adverse experiences was similar in patients taking rofecoxib or placebo, consistent with a lack of prothrombotic effect of rofecoxib even in high risk populations.

4.3.6 Rofecoxib Postmarketing Experience

Rofecoxib was first approved outside the U.S. for marketing on 01-Feb-1999 and by the FDA on 20-May-1999. Based on drug distribution data, assuming a single unit dose per day irrespective of the dosage strength, a total of 967,000 patient-treatment years of rofecoxib had been distributed worldwide as of 31-Jan-2000.

As of 13-Mar-2000, the company's Worldwide Adverse Experiences Surveillance (WAES) database for rofecoxib contained a total of 5576 spontaneous marketed-use adverse experience reports. Of these, 3491 were received from sources in the U.S. and 2085 from outside of the U.S. Among the 5576 total reports there were 617 (11.1%) which contained one or more adverse experiences codes mapping to the cardiovascular body system in the company's medical codes dictionary: 431 were received from sources in the U.S. and 186 were received from sources outside of the U.S. Seventy-eight of the 617 reports containing 1 or more cardiovascular adverse experience (1.4% of all reports) contained thrombotic adverse experiences terms as used throughout this report. There were 15 reports of myocardial infarction and 16 reports of cerebrovascular accidents.

Based on the above estimated distribution data, the 78 reports represent a reporting rate of 8.1 reports per 100,000 patient-treatment-years distributed. These reports are small in number relative to the background occurrence of such events in the age-group of patients in which rofecoxib is predominately prescribed. These data indicate that there is no signal of an unexpectedly high incidence of these types of events among the general population of patients taking rofecoxib.

RA patients present a higher risk group of patients for thrombotic cardiovascular serious adverse experiences. To determine if patients with RA are disproportionately represented among these 78 cases, the cases were reviewed and data were obtained about the use of rofecoxib in RA. Audited data from IMS, Inc. indicates that, in the U.S., 4.5% of rofecoxib use is in patients with RA. Review of the 78 reports described above indicates that a diagnosis of RA was reported in 4 patients (5.1% of 78). Thus, there is no evidence in these data for a disproportionate incidence in RA patients of thrombotic adverse experiences during the use of rofecoxib.

Patients with systemic lupus erythematosus are another group of patients at high risk for thrombotic cardiovascular serious adverse experiences who may have receive rofecoxib. In fact, Crofford et al. [95] reported a series of 3 patients with antiphospholipid antibody syndrome (APS) who developed acute peripheral thromboses and 1 who developed a pulmonary embolus shortly after starting treatment with celecoxib, another COX-2 selective inhibitor. These cases were in patients with multiple risk factors for thrombosis who were not receiving antiplatelet therapy. Because 20 to 35% of patients with systemic lupus erythematosus (SLE) are estimated to have APS, SLE patients were considered a population that merited additional investigation. Data from IMS, Inc. indicated that, through the end of Mar-2000, at least 31,000 patients in the U.S. received at least one prescription for rofecoxib for the indication "SLE". A search of the Merck WAES database (on 15-Jun-2000) for lupus-related terms identified 33 cases. There were 2 possible cases of thrombosis; in both a relationship with rofecoxib could not be established. One occurred in a patient with APS on long-term anticoagulation for recurrent pulmonary emboli who, 2 weeks after being hospitalized for correction of a highly elevated INR, had another pulmonary embolus. In this case, the correction of the INR and possible reversal of anticoagulation is the most likely cause of the recurrence of pulmonary emboli. The other report was of a patient with scleroderma who, in the setting of accelerated hypertension, had a trace elevated troponin-1 level which was thought to indicate a possible small MI. However, patients with scleroderma have microvascular disease and this type of event is typical of the course of the underlying disease process. A manual review of cases that included thrombotic terms failed to identify additional patients reported to have SLE, APS, or related syndromes.

Thus, even in populations of patients at increased risk for thrombotic cardiovascular events, no signal for a prothrombotic effect of rofecoxib has been identified in postmarketing adverse experience reports.

4.3.7 Conclusions—Cardiovascular Events

- The rates of thrombotic cardiovascular serious adverse experiences in patients taking rofecoxib are similar to those in patients taking the nonselective NSAIDs ibuprofen, diclofenac, or nabumetone.
- The rates of thrombotic cardiovascular serious adverse experiences in patients taking rofecoxib are similar to those in patients taking placebo, including elderly patients at relatively high risk for thrombotic cardiovascular serious adverse experiences.

- The rates of thrombotic cardiovascular serious adverse experiences are lower in patients treated with naproxen compared to rofecoxib. This difference in rates does not appear to be due to a prothrombotic effect of rofecoxib but rather a cardioprotective benefit of naproxen due to its potent and sustained antiplatelet effects.

4.4 Conclusions—Non-GI Safety

- The non-GI safety of rofecoxib in VIGOR was consistent both qualitatively and quantitatively with the previous experience in OA as reflected in the approved rofecoxib product label.
- Differences between the rofecoxib 50-mg and naproxen 1000-mg groups in the incidence of mechanism-based, dose-dependent adverse experiences (e.g., hypertension and edema) were consistent with the use of rofecoxib at 2 times its maximal approved dose for chronic administration.
- Discontinuations in VIGOR due to renal/vascular adverse experiences or due to alterations in laboratory measurements of liver function in patients taking rofecoxib 50 mg were rare and lower than in the rofecoxib 50-mg groups in the Phase III 6-Month OA Studies.
- In VIGOR, the incidence of thrombotic cardiovascular serious adverse experiences was lower in the naproxen group than in the rofecoxib group, consistent with the potent and sustained antiplatelet effects of naproxen and the lack of effect of rofecoxib on platelet function.
- In VIGOR, the incidence of non-GI bleeding events (ecchymoses and epistaxis) was less in patients taking rofecoxib than naproxen, consistent with the potent and sustained antiplatelet effects of naproxen and the lack of effect of rofecoxib on platelet function.
- Analysis of the incidence of thrombotic cardiovascular serious adverse experiences in other studies that did not use naproxen as a comparator demonstrate that the risk of these events in patients taking rofecoxib is the same as in patients receiving placebo or other nonselective NSAIDs, further substantiating the position that rofecoxib does not have a prothrombotic effect.
- Because rofecoxib has no effect on COX-1 at clinical doses, it does not have antiplatelet properties and therefore cannot substitute for low-dose aspirin in cardiovascular prophylaxis.

5. Summary

Rofecoxib is a highly selective COX-2 inhibitor at doses well in excess of the clinical range. In contrast, nonselective NSAIDs inhibit both COX-1 and COX-2 at clinical doses. The "COX-2 hypothesis" proposed that COX-2 is the isoenzyme important for generating prostaglandins that mediate inflammation, pain, and fever, whereas COX-1 produces prostaglandins important for "housekeeping" functions such as maintaining GI epithelial integrity and platelet aggregation. The COX-2 hypothesis predicted that a COX-2 selective inhibitor would be effective in treating pain, inflammation, and fever and would have a substantially improved GI safety profile compared with nonselective NSAIDs. A COX-2 selective inhibitor was also predicted to have no effect on platelet function. However, a difference in platelet effects between a highly selective COX-2 inhibitor and nonselective NSAIDs might prove to be clinically significant in patients at risk of thromboembolic events. With regard to adverse experiences due to the mechanism-based inhibition of COX-2, COX-2 selective inhibitors were predicted to have renal/vascular effects similar to nonselective COX-1/COX-2 inhibitors.

The rofecoxib development program has evaluated all of the predictions of the COX-2 hypothesis. Rofecoxib has been shown to relieve pain and inflammation and is approved for relief of the signs and symptoms of OA and for the treatment of acute pain and dysmenorrhea. The recommended starting dose in OA is 12.5 mg daily. Some patients may derive additional benefit from 25 mg. The recommended dose for the short-term treatment of acute pain or dysmenorrhea is 50 mg daily. In a Phase IIb dose-ranging study, rofecoxib 25 mg daily was shown to be superior to placebo and similar to rofecoxib 50 mg for the treatment of RA. Recent Phase III studies not yet reviewed by the FDA confirm that the anticipated dose for the treatment of RA with rofecoxib is 25 mg.

Rofecoxib had been shown in the OA development program to have significantly less GI toxicity than nonselective NSAIDs. The purpose of VIGOR was to provide conclusive evidence of the improved GI safety of rofecoxib compared with a standard, nonselective NSAID. VIGOR demonstrated, in RA patients, that rofecoxib 50 mg daily is associated with a 54 to 62% lower risk of clinical upper GI events, complicated upper GI events, and GI bleeds compared to naproxen 1000 mg daily. Rofecoxib demonstrated consistency of effect in reducing the risk of clinical upper GI events in all subgroups analyzed. In addition, rofecoxib use was associated with less upper GI nuisance-type symptoms and fewer discontinuations due to GI adverse experiences than nonselective NSAIDs. Consistent with this, patients taking rofecoxib used fewer gastroprotective agents and required fewer GI diagnostic procedures than patients taking nonselective NSAIDs. The risk reduction of clinical upper GI events in VIGOR was nearly identical to the risk reduction in rofecoxib-treated patients versus nonselective NSAID-treated patients in the combined analysis of all Phase IIb/III OA studies. These broad findings in different studies, at different doses of rofecoxib, and in both OA and RA populations indicate that the improved GI safety of rofecoxib relative to nonselective NSAIDs applies generally to patients who require chronic therapy with NSAIDs.

The non-GI safety profile of rofecoxib has been shown to be similar to nonselective NSAIDs. Adverse experiences associated with rofecoxib represent a subset of those described for the nonselective NSAIDs and the incidence of these events with rofecoxib is similar to the incidence with comparably-dosed nonselective NSAIDs. Studies have demonstrated that, like standard NSAIDs, rofecoxib is associated with dose-dependent renal/vascular effects (hypertension and edema), due to the mechanism-based inhibition of COX-2. The incidence of these events at the recommended chronic doses of rofecoxib (12.5 to 25 mg once daily) is similar to nonselective NSAIDs; the incidence is somewhat increased in patients administered 50 mg chronically. In general, the nature and incidence of renal/vascular effects were consistent between the VIGOR and Phase IIb/III OA studies and infrequently required the discontinuation of rofecoxib therapy. In addition, approximately 1% of patients taking recommended doses of rofecoxib (12.5 mg or 25 mg) experienced elevations in liver transaminases that were ≥3 times the upper limit of normal. The incidence of these increases was <1% in patients taking 50 mg rofecoxib in the VIGOR study. These elevations resolved in patients treated with rofecoxib, with approximately half resolving while patients remained on therapy. The frequency of such elevations in transaminases was similar to that with the nonselective NSAIDs ibuprofen and naproxen and significantly less than with diclofenac.

The aggregate of data from the rofecoxib development program in close to 30,000 patients supports the cardiovascular safety of rofecoxib. The risk of thrombotic events in patients taking rofecoxib is similar to placebo even in elderly patients at risk for such events. However, there were significantly fewer thrombotic cardiovascular serious adverse experiences (in general) and MI (in particular) in patients taking naproxen compared with rofecoxib. Naproxen is one of the few NSAIDs that provides potent and sustained antiplatelet effects similar to what is described for aspirin. As a highly selective COX-2 inhibitor, rofecoxib has no effect on platelet function. The VIGOR study results as analyzed in the context of the entire rofecoxib development program are most consistent with naproxen having provided a cardioprotective benefit to patients at risk for these events. As would be expected, the difference between rofecoxib and naproxen in the VIGOR study was most apparent in the 4% of patients who had symptomatic atherosclerotic cerebrovascular or coronary vascular disease and thus an indication for prophylactic antiplatelet therapy.

Thus, for patients with osteoarthritis who require chronic therapy with a NSAID, rofecoxib offers a clear GI safety advantage over nonselective NSAIDs. At recommended doses, rofecoxib is similar to nonselective NSAIDs with regard to efficacy and non-GI safety. Thus, the balance of risks and benefits favors the use of rofecoxib over nonselective NSAIDs.

In patients who require cardioprotective antiplatelet therapy, rofecoxib is clearly not a substitute for aspirin. In such patients, it is recommended that low-dose aspirin be taken concomitantly with rofecoxib. The relative risk of clinical GI events in patients taking rofecoxib plus aspirin versus a nonselective NSAID (such as naproxen) has not been

determined. Determination of this relative risk with reasonable precision at a statistically significant level of $p<0.05$ would require a study of over 20,000 patients. Recent data show, however, that the risk of GI bleeding with doses of aspirin ≤300 mg/day is about a third of that associated with nonselective NSAIDs [96]. Thus, it is reasonable to conclude that the risk of a GI event would be lower with rofecoxib plus aspirin as compared to a nonselective NSAID such as naproxen taken with or without aspirin. MRL is currently conducting a 12-week endoscopic ulcer surveillance study to determine the incidence rates of ulcers in patients taking rofecoxib 25 mg daily plus low-dose aspirin, low-dose aspirin alone, ibuprofen 800 mg 3 times daily, or placebo,. From a cardioprotection standpoint, it is also reasonable to recommend rofecoxib plus low-dose aspirin over a nonselective NSAID such as naproxen for the following reasons: (1) the antiplatelet effects of aspirin persist several days after aspirin is taken whereas the antiplatelet effects of a nonselective NSAID, even one with relatively prolonged effects, will diminish with time – thus with aspirin, there is greater margin for error with regard to missed doses; (2) there is extensive experience with aspirin as a cardiovascular protective agent; and (3) rofecoxib has been shown not to interfere with the antiplatelet effects of aspirin. Thus, the balance of risks and benefits for the patient population with an indication for both rofecoxib and aspirin therapy favors a recommendation of rofecoxib plus low-dose aspirin over the use of a nonselective NSAID either alone or in combination with aspirin, although the magnitude of the GI benefit of rofecoxib plus aspirin over nonselective NSAIDs may be less than the benefit of rofecoxib taken without aspirin.

In summary, rofecoxib provides efficacy similar to nonselective NSAIDs with reduced GI toxicity, the most common NSAID-related toxicity associated with serious outcomes. Rofecoxib otherwise manifests a comparable incidence of non-GI adverse experiences as observed with nonselective NSAIDs. Therefore, in patients in whom chronic therapy with a COX inhibitor is indicated, rofecoxib represents a clinically important improvement over nonselective NSAIDs.

6. Overall Conclusions

Rofecoxib has efficacy similar to nonselective NSAIDs in OA and acute analgesia and is approved for the relief of the signs and symptoms of OA and for the treatment of acute pain and primary dysmenorrhea. The maximally recommended chronic dose for OA is 25 mg daily. The anticipated dose for the relief of the signs and symptoms of RA with rofecoxib is also 25 mg daily.

The Results of VIGOR Confirm That Rofecoxib has a GI Safety Profile Superior to Nonselective NSAIDs

- In RA patients, rofecoxib 50 mg daily (2 to 4 times the recommended dose in OA and 2 times the anticipated dose in RA) is associated with significantly fewer clinical upper GI events, complicated upper GI events, and GI bleeding than 1000 mg daily of the nonselective NSAID naproxen. The risk reduction with rofecoxib in VIGOR ranged from 54% for confirmed clinical upper GI events to 62% for any GI bleed.
- In OA patients, rofecoxib at an average dose of 24.7 mg daily, is associated with significantly fewer clinical upper GI events than nonselective NSAIDs. The risk reduction with rofecoxib in the combined analysis of all Phase IIb/III OA studies was 55%.
- Rofecoxib 25 mg and 50 mg daily are associated with significantly fewer endoscopic ulcers in OA patients than ibuprofen 2400 mg daily.
- The improved GI safety of rofecoxib compared with nonselective NSAIDs is observed in the entire OA and RA patient populations and in high-risk subgroups, including the elderly, corticosteroid users, H. pylori-positive patients, and patients with a prior history of a clinical upper GI event.
- These broad findings in different studies, at different doses, and in both OA and RA populations indicate that the improved GI safety of rofecoxib relative to nonselective NSAIDs applies generally to patients who require chronic therapy with NSAIDs.

These results support deletion of the NSAID-class GI *Warning* from the rofecoxib U.S. Product Circular and a description of the GI effects in the label. This will serve to appropriately distinguish rofecoxib from nonselective NSAIDs.

The Results of VIGOR Confirm the General Safety Profile of Rofecoxib as Presented in the Currently Approved Product Circular

- The non-GI safety of rofecoxib in VIGOR was consistent both qualitatively and quantitatively with the previous experience in OA at the 50-mg dose and with the approved rofecoxib product label.
- Differences between the rofecoxib 50-mg daily and naproxen 1000-mg daily group in the incidence of mechanism-based, dose-dependent adverse experiences (e.g., hypertension and edema) were consistent with the use of rofecoxib at 2 times its maximal approved dose for chronic administration.

- Discontinuations in VIGOR due to renal/vascular adverse experiences or due to alterations in laboratory measurements of liver function in patients taking rofecoxib were rare and lower than in the Phase III 6-Month OA Studies.
- In VIGOR, the incidence of serious thrombotic cardiovascular events was lower in the naproxen group than in the rofecoxib group, consistent with the potent and sustained antiplatelet effects of naproxen and the lack of effect of rofecoxib on platelet function.
- Analyses of the incidence of thrombotic cardiovascular events in other studies that did not use naproxen as a comparator demonstrate that the risk of these events in patients taking rofecoxib is the same as in patients receiving placebo or other nonselective NSAIDs.
- Because rofecoxib has no effect on COX-1 at clinical doses, it does not have antiplatelet properties and therefore cannot substitute for aspirin in cardiovascular prophylaxis.

The difference in antiplatelet activity between nonselective NSAIDs with potent and sustained COX-1 inhibiting activity and selective COX-2 inhibitors may be of clinical significance in patients at risk for thromboembolic events. The results of VIGOR emphasize the existing labeling statement that rofecoxib is not a substitute for aspirin for cardiovascular prophylaxis. It is recommended that patients who require low-dose aspirin therapy for cardiovascular prophylaxis should continue on aspirin during therapy with rofecoxib.

Overall Conclusion

The high degree of consistency throughout all studies in the GI safety program and the nearly identical reduction in the relative risk of clinical upper GI events and complicated upper GI events in the combined analysis of the Phase IIb/III OA program and in VIGOR speaks strongly for the robustness of these data and confirms the conclusions of the individual studies. Thus, overall, it is concluded:

- Rofecoxib, a highly selective COX-2 inhibitor, provides efficacy similar to nonselective NSAIDs but with significantly less gastropathy, significantly fewer clinical upper GI events, and significantly fewer clinically complicated upper GI events than nonselective NSAIDs.

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APPENDIX 1

VIGOR Endpoint Adjudication Criteria

Event	Criteria For Confirmed Event	Criteria For Confirmed Complicated Event
Gastric or Duodenal Perforation due to Active Gastric Ulcer (GU) or Duodenal Ulcer (DU)	Report of gastric or duodenal perforation (excluding perforation caused by a malignant ulcer) confirmed by one or more of the following: 1. Endoscopy 2. Surgery 3. Unequivocal radiographic results consistent with free intraperitoneal air or extravasation of contrast media 4. Autopsy	All gastric or duodenal perforations are classified as complicated.
Obstruction due to Active Gastric Ulcer (GU) or Duodenal Ulcer (DU)	Postprandial nausea and vomiting lasting for at least 24 hours **AND** evidence of narrowing of the distal stomach, pylorus, or duodenum due to a non-malignant ulcer documented by: 1. Endoscopy 2. Surgery 3. Radiography 4. Autopsy	All obstructions are classified as complicated
Development of Active Gastric Ulcer (GU) or Duodenal Ulcer (DU)	Report of GU or DU confirmed by one or more of the following: 1. Endoscopy 2. Surgery 3. Unequivocal radiological evidence of active GU or DU on upper-GI series with contrast 4. Autopsy	GU or DU associated with a confirmed upper-GI hemorrhage as defined under Development of Upper-GI Hemorrhage, criteria 1, 2, or 3[†].

APPENDIX 1 (CONT.)

VIGOR Endpoint Adjudication Criteria

Event	Criteria For Confirmed Event	Criteria For Confirmed Complicated Event
Development of Upper-GI (esophageal, gastric, or duodenal) Hemorrhage	Report of upper-GI hemorrhage fulfilling one or more of the following: 1. Healthcare provider witnessed frank hematemesis (distinguished from blood tinged or streaked emesis), including coffee-grounds vomitus, **OR** healthcare provider-witnessed frank blood or coffee grounds by gastric aspiration or lavage (distinguished from scant coffee-grounds that clear rapidly). 2. Healthcare provider witnessed frank melena (distinguished from other dark stool e.g., that due to bismuth salts). 3. Active upper-GI bleeding documented by endoscopy, angiography, or surgery. 4. Heme-positive stool associated with a documented upper-GI lesion judged by the healthcare provider to be the source of the bleeding **AND** associated with either of the following: a) Significant bleeding/volume loss b) Stigmata of recent bleeding (visible vessel, pigmented spot or clot on ulcer base) on endoscopy.	1. Upper-GI hemorrhage associated with significant bleeding/volume loss (1).

APPENDIX 1 (CONT.)

VIGOR Endpoint Adjudication Criteria

Event	Criteria For Confirmed Event	Criteria For Confirmed Complicated Event
Development of Upper-GI (esophageal, gastric, or duodenal) Hemorrhage (Cont.)	5. Patient‡ reported hematemesis or melena associated with a documented upper-GI lesion judged by the healthcare provider to be the source of the bleeding **AND** associated with one or more of the following: a) Significant bleeding/volume loss b) Stigmata of recent bleeding (visible vessel, pigmented spot or clot on ulcer base) on endoscopy.	
(1) Criteria for significant bleeding/volume loss: One or more of the following (a, b, c, or d) is temporally related to the event: a. Decrease in hemoglobin ≥2 gm/dL (or ≥6% drop in hematocrit if hemoglobin not available). b. Evidence of orthostatic (sitting to standing, or lying to sitting) changes; one or more of: i) pulse rate increase of >20 BPM, ii) decrease in SBP >20 mm Hg, iii) decrease in DBP >10 mm Hg. c. Other evidence of significantly reduced circulatory volume (e.g., significant hypotension corrected by volume replacement). d. Transfusion of blood or packed red blood cells.		
Differences between the VIGOR criteria and those used in the combined analysis of the OA Phase IIb/III Program: † Complicated ulcers in the OA analysis included "giant" ulcers (gastric ulcer ≥3 cm or duodenal ulcer ≥2 cm). ‡ In the OA analysis, bleeding had to be documented by the investigator. In addition, the OA analysis did not provide for the classification of an event as "not an upper GI event."		

APPENDIX 2

Final Serious Thromboembolic Cardiovascular Terms Eligible for Case Adjudication

Acute myocardial infarction
Angina pectoris
Anterior spinal artery obstruction
Aortoiliac obstruction
Arterial embolism
Arterial occlusion
Arterial thrombosis
Basilar artery obstruction
Brachial artery occlusion
Cardiac arrest
Cardiac catheter Complication
Cardiac stress test abnormality
Cardiac thrombosis
Cardiogenic shock
Cardiovascular disorder
Cardiovascular hemodynamics abnormality
Carotid artery disorder
Carotid artery obstruction
Cerebellar artery obstruction
Cerebellar hemorrhage
Cerebral artery obstruction
Cerebral atherosclerosis
Cerebral hypoxia
Cerebral infarction
Cerebral ischemia
Cerebral thrombosis
Cerebrovascular accident
Cerebrovascular disorder
Coronary artery disease
Coronary artery occlusion
Coronary artery stenosis
Coronary vasospasm
Coronary vessel surgery complication
Cyanosis
Deep venous thrombosis
Electrocardiographic abnormality
Embolic stroke
Embolism
Endocardial disorder
Endocardial thrombus
Extracranial artery obstruction
Extradural hemorrhage
Femoral artery occlusion
Gangrene
Iliac artery occlusion
Intermittent claudication
Intracranial hemorrhage
Intracranial venous sinus phlebitis
Ischemic heart disease
Lacunar infarction
Lower extremity arterial occlusion
Lower extremity ischemia
Myocardial infarction
Myocardial infarction complication
Myocardial reinfarction
Myocardial rupture
Non-Q-wave myocardial infarction
Nonspecific ST-T change
Old myocardial infarction
Papillary muscle disorder
Peripheral ischemia
Peripheral pulse absent
Peripheral pulse decreased
Peripheral vascular disorder
Popliteal artery occlusion
Pulmonary embolism
Pulmonary infarction
Pulmonary thrombosis
Pulmonary vascular disease
Pulmonary veno-occlusive disease
Pulse absent
Q-wave abnormality
Q-wave myocardial infarction
QRS complex abnormality
Shock
Sinus thrombosis
Small vessel disease
ST segment abnormality
ST segment depression
ST segment elevation
ST-T change compatible with ischemia
Subclavian steal syndrome
Sudden death
Superior vena cava thrombosis t-wave abnormality
T-wave flat
T-wave inversion
Thromboembolic stroke
Thromboembolism
Thrombolysis
Thrombophlebitis
Thrombophlebitis migrans
Thrombosis
Thromboembolic microangiopathy
Transient ischemic attack
Ulnar artery occlusion
Unstable angina
Upper extremity arterial occlusion
Upper extremity ischemia
Vascular disorder
Vascular graft occlusion
Vascular insufficiency
Vascular occlusion
Vasospasm
Venous compression
Venous disorder
Venous occlusion
Venous thrombosis
Ventricular fibrillation
Ventricular flutter
Ventricular tachycardia
Ventricular thrombus
Vertebral artery obstruction
Vertebrobasilar insufficiency

APPENDIX 3

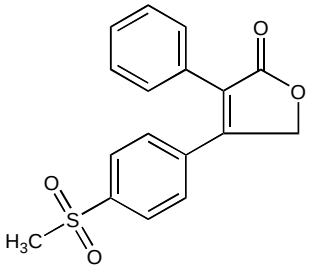
Approved U.S. Product Circular for Rofecoxib

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

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 $C_{17}H_{14}O_4S$, 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_{max}) following a single 25-mg dose were 3286 (±843) ng•hr/mL and 207 (±111) ng/mL, respectively. Both C_{max} and AUC are roughly dose proportional across the clinical dose range. At doses greater than 50 mg, there is a less than proportional increase in C_{max} and AUC, which is thought to be due to the low solubility of the drug in aqueous media. The plasma concentration-time profile exhibited multiple peaks. The median time to maximal concentration (T_{max}), as assessed in nine pharmacokinetic studies, is 2 to 3 hours. Individual T_{max} values in these studies ranged between 2 to 9 hours. This may not reflect rate of absorption as T_{max} may occur as a secondary peak in some individuals. With multiple dosing, steady-state conditions are reached by Day 4. The $AUC_{0\text{-}24hr}$ and C_{max} at steady state after multiple doses of 25 mg rofecoxib was 4018 (±1140) ng•hr/mL and 321 (±104) ng/mL, respectively. The accumulation factor based on geometric means was 1.67.

VIOXX Tablets 12.5 mg and 25 mg are bioequivalent to VIOXX Oral Suspension 12.5 mg/5 mL and 25 mg/5 mL, respectively.

*Registered trademark of MERCK & CO., Inc., Whitehouse Station, New Jersey, USA

Food and Antacid Effects

Food had no significant effect on either the peak plasma concentration (C_{max}) or extent of absorption (AUC) of rofecoxib when VIOXX tablets were taken with a high fat meal. The time to peak plasma concentration (T_{max}), however, was delayed by 1 to 2 hours. The food effect on the suspension formulation has not been studied. VIOXX tablets can be administered without regard to timing of meals.

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

Distribution

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

Rofecoxib has been shown to cross the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

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

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

Excretion

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

The plasma clearance after 12.5- and 25-mg doses was approximately 141 and 120 mL/min, respectively. Higher plasma clearance was observed at doses below the therapeutic range, suggesting the presence of a saturable route of metabolism (i.e., 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 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.

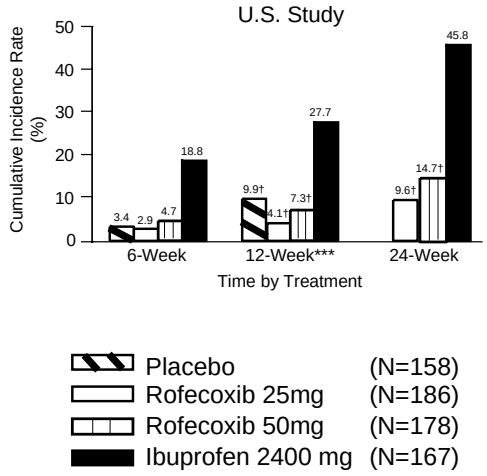
Treatment with VIOXX 25 mg daily or 50 mg daily was associated with a significantly lower percentage of patients with endoscopic gastroduodenal ulcers than treatment with ibuprofen 2400 mg daily. However, the studies cannot rule out at least some increase in the rate of endoscopic gastroduodenal ulcers 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

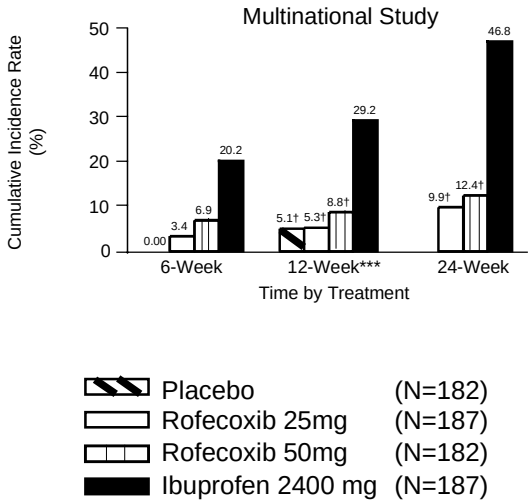
Treatment Group	Number of Patients with Ulcer/Total Number of Patients	Cumulative Incidence Rate*	Ratio of Rates vs. Placebo	95% CI on Ratio of Rates
Placebo	11/158	9.9%	–	–
VIOXX 25 mg	7/186	4.1%	0.41	(0.16, 1.05)
VIOXX 50 mg	12/178	7.3%	0.74	(0.33, 1.64)
Ibuprofen	42/167	27.7%	2.79	(1.47, 5.30)

*by life table analysis

Figure 2

COMPARISON TO IBUPROFEN

Life-Table Cumulative Incidence Rate of Gastroduodenal Ulcers ≥ 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 2
Endoscopic Gastroduodenal Ulcers at 12 weeks
Multinational Study

Treatment Group	Number of Patients with Ulcer/Total Number of Patients	Cumulative Incidence Rate*	Ratio of Rates vs. Placebo	95% CI on Ratio of Rates
Placebo	5/182	5.1%	–	–
VIOXX 25 mg	9/187	5.3%	1.04	(0.36, 3.01)
VIOXX 50 mg	15/182	8.8%	1.73	(0.65, 4.61)
Ibuprofen	49/187	29.2%	5.72	(2.36, 13.89)

*by life table analysis

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}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, anaphylactic-like reactions to NSAIDs have been reported in such patients (see WARNINGS, *Anaphylactoid Reactions* and PRECAUTIONS, *Preexisting Asthma*).

WARNINGS

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

Serious gastrointestinal toxicity such as bleeding, ulceration, and perforation of the stomach, small intestine or large intestine, can occur at any time, with or without warning symptoms, in patients treated with nonsteroidal anti-inflammatory drugs (NSAIDs). Minor upper gastrointestinal problems, such as dyspepsia, are common and may also occur at any time during NSAID therapy. Therefore, physicians and patients should remain alert for ulceration and bleeding, even in the absence of previous GI tract symptoms. Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months,

and in about 2-4% of patients treated for one year. These trends continue thus, increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

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_2 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_{max} of rofecoxib by 21%, the $AUC_{0\text{-}120hr}$ by 23% and the $t_{1/2}$ by 15%. These small changes are not clinically significant and no dose adjustment is necessary.

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

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

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

Lithium: NSAIDs have produced an elevation of plasma lithium levels and a reduction in renal lithium clearance. Thus, when VIOXX and lithium are administered concurrently, subjects should be observed carefully for signs of lithium toxicity.

Methotrexate: VIOXX 75 mg administered once daily for 10 days increased plasma concentrations by 23% as measured by $AUC_{0\text{-}24hr}$ in patients receiving methotrexate 7.5 to 15 mg/week for rheumatoid arthritis. An equivalent magnitude of reduction in methotrexate renal clearance was observed. At 24 hours postdose, a similar proportion of patients treated with methotrexate alone (94%) and subsequently treated with methotrexate co-administered with 75 mg of rofecoxib (88%) had methotrexate plasma concentrations below the measurable limit (5 ng/mL). 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 prednisolone or prednisone.

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

Warfarin: Anticoagulant activity should be monitored, particularly in the first few days after initiating or changing VIOXX therapy in patients receiving warfarin or similar agents, since these patients are at an increased risk of bleeding complications. In single and multiple dose studies in healthy subjects receiving both warfarin and rofecoxib, prothrombin time (measured as INR) was increased by approximately 8% to 11%. In post-marketing experience, bleeding events have been reported, predominantly in the elderly, in association with increases in prothrombin time in patients receiving VIOXX concurrently with warfarin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

Pregnancy

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_{0-24}). There was a slight, non-statistically significant increase in the overall incidence of vertebral malformations only in the rabbit at doses of 50 mg/kg/day (approximately 1- or <1-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). 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_{0-24} at 25 and 50 mg daily). These changes are expected with inhibition of prostaglandin synthesis and are not the result of permanent alteration of female reproductive function. There was an increase in the incidence of postnatal pup mortality in rats at ≥5 mg/kg/day (approximately 5- and 2-fold human exposure at 25 and 50 mg daily based on AUC_{0-24}). In studies in pregnant rats administered single doses of rofecoxib, there was a treatment-related decrease in the diameter of the ductus arteriosus at all doses used (3-300 mg/kg: 3 mg/kg is approximately 2- and <1-fold human exposure at 25 or 50 mg daily based on AUC_{0-24}). As with other drugs known to inhibit prostaglandin synthesis, use of VIOXX during the third trimester of pregnancy should be avoided.

Labor 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_{0-24} at 25 and 50 mg). The effects of VIOXX on labor and delivery in pregnant women are unknown.

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

Nursing mothers

Rofecoxib is excreted in the milk of lactating rats at concentrations similar to those in plasma. There was an increase in pup mortality and a decrease in pup body weight following exposure of pups to milk from dams administered VIOXX during lactation. The dose tested represents an approximate 18- and 6-fold human exposure at 25 and 50 mg based on AUC_{0-24}. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from VIOXX, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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	VIOXX 12.5 or 25 mg daily	Ibuprofen 2400 mg daily	Diclofenac 150 mg daily
	(N = 783)	(N = 2829)	(N = 847)	(N = 498)
Body As A Whole/Site Unspecified				
Abdominal Pain	4.1	3.4	4.6	5.8
Asthenia/Fatigue	1.0	2.2	2.0	2.6
Dizziness	2.2	3.0	2.7	3.4
Influenza-Like Disease	3.1	2.9	1.5	3.2
Lower Extremity Edema	1.1	3.7	3.8	3.4
Upper Respiratory Infection	7.8	8.5	5.8	8.2
Cardiovascular System				
Hypertension	1.3	3.5	3.0	1.6
Digestive System				
Diarrhea	6.8	6.5	7.1	10.6
Dyspepsia	2.7	3.5	4.7	4.0
Epigastric Discomfort	2.8	3.8	9.2	5.4
Heartburn	3.6	4.2	5.2	4.6
Nausea	2.9	5.2	7.1	7.4
Eyes, Ears, Nose, And Throat				
Sinusitis	2.0	2.7	1.8	2.4
Musculoskeletal System				
Back Pain	1.9	2.5	1.4	2.8
Nervous System				
Headache	7.5	4.7	6.1	8.0
Respiratory System				
Bronchitis	0.8	2.0	1.4	3.2
Urogenital System				
Urinary Tract Infection	2.7	2.8	2.5	3.6

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, chills, contusion, cyst, diaphragmatic hernia, fever, fluid retention, flushing, fungal infection, infection, laceration, pain, pelvic pain, peripheral edema, postoperative pain, syncope, trauma, upper extremity edema, viral syndrome.

Cardiovascular System: angina pectoris, atrial fibrillation, bradycardia, hematoma, irregular 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, dysgeusia, esophagitis, flatulence, gastric disorder, gastritis, gastroenteritis, hematochezia, hemorrhoids, infectious gastroenteritis, oral infection, oral lesion, oral ulcer, vomiting.

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

Immune System: allergy, hypersensitivity, insect bite reaction.

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

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

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

Psychiatric: anxiety, depression, mental acuity decreased.

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

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

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

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

Cardiovascular: cerebrovascular accident, congestive heart failure, deep venous thrombosis, 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.

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.

No. 3811 - Tablets VIOXX, 25 mg, are yellow, round, tablets engraved MRK 110 on one side and VIOXX on the other. They are supplied as follows:

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

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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