

No. COX 04-063  
Aug 26, 2004

**BULLETIN FOR VIOXX:**  
**Action Required: Observational Analysis by Graham et. al.**

**TO:**

Primary Care Representatives with Responsibility for VIOXX	Action Required
A & A Specialty Representatives	Action Required
Hospital Representatives with Responsibility for VIOXX	Action Required
A & A HSAs	Action Required
Neurology/Urology Specialty Representatives	Action Required
HIV Specialty Representatives	Action Required
Cardiovascular Specialty Representatives	Action Required
Managed Care NAEs and Customer Managers	Action Required

**PURPOSE:**

To notify you that a recent observational analysis by D.J.Graham, et al, was presented in France at the International Society for Pharmacoepidemiology Conference. This analysis questioned the safety of VIOXX and is expected to receive press coverage. This bulletin will provide you with an issue response letter that you may provide to your customers only if they raise a question about the study.

**ACTION REQUIRED:**

- Do not proactively raise this article with your physicians. Respond to questions only as set forth in the attachments
- Use the following issue response when asked an unsolicited question by a physician regarding this article
- Return to your entire, well-balanced efficacy story for VIOXX once the obstacle is addressed
- Do not deviate from the language in this obstacle response
- Remember to provide appropriate balancing information as part of all product discussions

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**ISSUE RESPONSE:**

**There is an observational analysis that says VIOXX causes more CV events than Celebrex.**

<p>1. Merck stands behind the overall safety of VIOXX</p>	<p>First, Dr, let me say that based on all of the data that are available, Merck stands behind the overall efficacy and safety profile of VIOXX. Based on all of the available data, VIOXX remains an excellent choice for your appropriate patients.</p>
<p>2. Interpret with caution</p>	<p>Merck believes that conclusions from retrospective, observational analyses should be interpreted with caution. Observational studies, even those conducted in as rigorous a manner as possible, are often unable to completely control for differences between groups, which may produce confounded results. These types of analyses must always be considered in light of their limitations and within the context of randomized, controlled clinical trials. For example, epidemiological analyses showed that use of hormone replacement therapy was associated with a reduced risk of heart attack and death. This influenced clinical practice for years. However, data from the Women's Health Initiative, a landmark randomized clinical trial, have shown that hormone replacement therapy was not associated with a cardiovascular benefit.</p>
<p>3. Review Precautions Section of Label for VIOXX GI Outcomes Research Study</p>	<p>Doctor, let me review the cardiovascular effects section of the VIOXX label.</p> <ul style="list-style-type: none"><li>- In the VIOXX GI Outcomes Research Study, 8076 rheumatoid arthritis patients (mean age 58) were followed for an average of 9 months.</li><li>- Cardiovascular thrombotic events were 45 for VIOXX 50mg qd as compared to 19 for naproxen 500mg bid, largely due to nonfatal myocardial infarction (18 vs. 4)</li><li>- Mortality due to cardiovascular thrombotic events (7 vs 6, VIOXX vs naproxen respectively) was similar between the treatment groups.</li></ul>
<p>4. Review Precautions Section of Label for Placebo-Controlled Trials</p>	<p>The VIGOR study did not include a non-naproxen NSAID comparator, so let me review data from long-term placebo-controlled trials that is also included in the label for VIOXX.</p> <ul style="list-style-type: none"><li>- In a placebo-controlled trials database derived from 2 studies with a total of 2142 elderly patients (mean age 75) followed for an average of 14 months.</li><li>- Serious cardiovascular thrombotic events were 21 vs 35 for patients treated with VIOXX 25mg qd vs placebo, respectively.</li><li>- Mortality due to cardiovascular thrombotic events was 8 vs 3 for VIOXX vs placebo, respectively.</li></ul>
<p>5. Significance Unknown</p>	<p>As stated here in the label, the significance of the cardiovascular findings from these 3 studies is unknown.</p>



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<p>6. VIOXX is not a replacement for aspirin</p>	<p>Because of its lack of platelet effects, VIOXX is not a substitute for aspirin for cardiovascular prophylaxis. Therefore, in patients taking VIOXX, anti-platelet therapies should not be discontinued and should be considered in patients with an indication for cardiovascular prophylaxis.</p>
<p>7. Merck is conducting more studies</p>	<p>Lastly Dr., Merck is conducting large prospective randomized clinical trials that when added to the extensive data from controlled clinical trials that are already available, will provide an even more comprehensive picture of the cardiovascular safety profile of VIOXX.</p>
<p>8. Response letter and transition</p>	<p>If your customer continues to have questions, you may leave a copy of the letter in response to DJ Graham's analysis. Then transition to your core messages based on your physician's beliefs.</p>

**ISSUES RESPONSE LETTER:**

- Do not proactively raise this topic with your customers
- You may print the attached letter and hand it out to your customers, when appropriate, along with a copy of the current PI for VIOXX.



Issue Resonse Letter

For product and service information, call the Merck National Service Center at 1-800-NSC MERCK (1-800-672-6372).



\*\*\* Slip Sheet \*\*\*

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Child

Merck & Co., Inc.  
U.S. Human Health  
P.O. Box 1000  
North Wales, PA 19454-1099



**Merck Strongly Disagrees with Conclusions of Observational Analysis  
Presented at International Medical Meeting**

Dear Healthcare Professional:

Nothing is more important to Merck than the safety of its medicines. Merck stands behind the efficacy, overall safety, and cardiovascular safety of VIOXX<sup>®</sup> (rofecoxib).

You have asked about one of the observational analyses presented recently in France at the International Society for Pharmacoepidemiology conference. In the observational study by D.J. Graham et al, the authors questioned the safety of VIOXX and other NSAIDs.

Observational studies, even those conducted in as rigorous a manner as possible, are often unable to completely control for differences between groups, which may produce confounded results. These types of analyses must always be considered in light of their limitations and within the context of randomized, controlled clinical trials. For example, epidemiologic analyses showed that use of hormone replacement therapy was associated with a reduced risk of heart attack and death. This influenced clinical practice for years. However, data from the Women's Health Initiative, a landmark randomized clinical trial, have shown that hormone replacement therapy was not associated with a cardiovascular benefit.

Prospective, randomized, controlled clinical trials are the gold standard to evaluate the safety and efficacy of any medicine. The available prospective clinical data support the safety and efficacy of VIOXX. VIOXX has been extensively studied and more than 24,000 patients have been treated with VIOXX in randomized, controlled clinical trials. Based on all of the available data, VIOXX remains an excellent choice for your appropriate patients.

Although the study was funded by the US Food and Drug Administration, the conclusions presented by the authors do not necessarily reflect the views of the FDA.

VIOXX is indicated for relief of the signs and symptoms of osteoarthritis (OA), relief of the signs and symptoms of rheumatoid arthritis (RA) in adults, management of acute pain in adults, treatment of primary dysmenorrhea, and acute treatment of migraine attacks with or without aura in adults. The safety and effectiveness of VIOXX have not been established for cluster headache, which is present in an older, predominantly male, population.

**Selected Safety Information**

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

VIOXX should not be given to patients who have experienced asthma, urticaria, or allergic-type reactions after taking aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs). Severe, rarely fatal, anaphylactic-like reactions to NSAIDs have been reported in such patients.

In the VIGOR Study, which involved more than 8,000 RA patients, VIOXX® (rofecoxib) 50 mg once daily, twice the recommended chronic dose, reduced the risk of clinically significant gastrointestinal (GI) events by 54% compared with naproxen 500 mg bid.

Also in the VIGOR Study, the risk of a serious cardiovascular (CV) thrombotic event on VIOXX 50 mg was higher than with naproxen (45 vs 19, respectively [ $P < 0.002$ ]), largely due to nonfatal myocardial infarction (18 vs 4). CV mortality was similar (7 on VIOXX vs 6 on naproxen).

In 2 long-term (median 14 months) studies involving elderly patients (N=2,142, mean age 75), the number of serious CV thrombotic events in patients on VIOXX 25 mg compared with placebo was 21 vs 35, and mortality due to these events was 8 vs 3, respectively.

The clinical significance of the CV findings from these 3 studies is unknown.

**Because of its lack of effects on platelets, VIOXX is not a substitute for aspirin for CV prophylaxis.**

Caution should be exercised when VIOXX is used in patients with a medical history of ischemic heart disease.

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

In RA studies of at least 3 months (which included extensions of up to 1 year), the adverse-event profile was generally similar to that reported in the OA studies; the incidence of hypertension in RA patients was 10.0% with VIOXX 25 mg qd and 4.7% with naproxen 500 mg bid.

In OA and RA clinical trials of VIOXX 12.5 mg or 25 mg, as well as 50 mg, VIOXX 50 mg qd was associated with a higher incidence of GI symptoms, lower extremity edema, hypertension, serious adverse experiences, and discontinuation due to clinical adverse experiences. For additional information, see the Adverse Reactions section of the Prescribing Information.

In OA, the recommended starting dose is 12.5 mg once daily. Some patients may receive additional benefit by increasing the dose to 25 mg once daily, the maximum recommended dose.

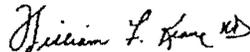
In RA, the recommended dose is 25 mg once daily. The maximum recommended daily dose is 25 mg.

In acute pain and in primary dysmenorrhea, the recommended dose of VIOXX is 50 mg once daily. The maximum recommended daily dose is 50 mg. Use of VIOXX for more than 5 days in management of acute pain has not been studied. Chronic use of VIOXX 50 mg daily is not recommended.

In acute treatment of migraine attacks with or without aura, the recommended starting dose of VIOXX is 25 mg once daily. Some patients may receive additional benefit with 50 mg as compared to 25 mg. The maximum recommended daily dose is 50 mg. The safety of treating more than 5 migraine attacks in any given month has not been established. Chronic daily use of VIOXX for acute treatment of migraine is not recommended.

Before prescribing VIOXX, please read the accompanying Prescribing Information.

Sincerely,



William F. Keane, MD  
Vice President  
US Medical and Scientific Affairs