

No. COX 01-030
May 23, 2001

Bulletin for VIOXX®:
Action Required: Response to New York Times Article

TO:

All Field Representations with Responsibility for VIOXX	Action Required
All Hospital Representatives	Action Required
A & A Specialty Representatives	Action Required
A & A HSAs	Action Required
Urology Representatives	Action Required
Neurology Representatives	Action Required
Managed Care NAEs and Customer Managers (all segments)	Background Information

DO NOT INITIATE DISCUSSIONS ON THE RESULTS OF THE VIOXX® GI OUTCOMES RESEARCH (VIGOR) STUDY, OR ANY OF THE RECENT ARTICLES IN THE PRESS ON VIOXX. YOU MAY RESPOND TO CUSTOMER INQUIRIES ONLY AS OUTLINED BELOW.

PURPOSE:

To provide you with important background information, obstacle responses and faxable PIR instructions in the event that you are questioned by customers about the CV effects of VIOXX.

ACTIONS REQUIRED:

Obstacle Response #38: (originally issued in Bulletin COX 00-029)



"Doctor, there are no head-to-head studies comparing the cardiovascular profile of the two drugs. As a result, you cannot compare the drugs and conclude that one drug had fewer events than the other. What you may be referring to is press reports of the incidence rates in two separate studies. In the VIOXX GI Outcomes Trial (VIGOR), the incidence of MI was 0.5% with VIOXX and 0.1% with naproxen. In a separate GI outcomes trial of Celebrex, the CLASS study, Searle has reported that the incidence of MI was 0.5% with Celebrex, 0.3% with diclofenac, and 0.5% with ibuprofen. Again, doctor, I want to emphasize that the results of two different studies can't be compared, and that's particularly true here when you have studies of differing duration and in different patient populations."

If the doctor asks you further for the incidence of MI from the OA studies presented in the package insert for VIOXX tell them:

"In the clinical OA trials for VIOXX reported in our package insert, the incidence of MI was less than 0.1% with VIOXX."

Use your CV Card to show the data on studies involving VIOXX and various NSAIDs (ibuprofen, diclofenac, and nabumetone) on overall mortality and CV mortality rates

"Doctor, As you can see, Cardiovascular Mortality as reported in over 6,000 patients was VIOXX .1 vs. NSAIDs .8 vs. Placebo 0."

Physician Inquiries:

In response to unsolicited requests for information regarding the recent press releases, Medical Services will make a personalized, faxable PIR available for your customers within 24 hours. In addition, for those customers who request more detailed information, a separate, more comprehensive PIR packet can be Federal Expressed within 2 days.

Medical Services has made arrangements to extend the hours for the PIR hotline. Representatives should submit unsolicited PIR requests by either telephone or fax options by calling the PIR hotline 800MERCK66 (800-637-2566) during extended hours of 8:30 am to 6:30pm ET. During these hours, a staff member will verbally request the following information from you to process the PIR request from the HCP [After this time, the usual method options of INSIGHT, PIR hotline (800MERCK 66 – hours: 8:30 – 4:30pm ET) and fax can be followed].

Faxable PIR Instructions:

- Your name, field title and RDT
- The requesting HCP's full name and professional degree
- HCP's full mailing address
- HCP's phone number
- HCP's FAX number
- Provide the question(s) asked by the HCP.

PIR Requests may also be sent to Medical Services from 4:30 pm – 8:30am ET by leaving a voice message at 800MERCK66. The information as listed above should be provided in your voice message to Medical Services staff. Additionally, PIR requests may be submitted to Medical Services in writing by sending a fax to 800MERCK68. The information listed above should be included on your fax to Medical Services.

- If requested, a PIR will be faxed within 24 hours of receiving the request.
- If the physician requests more comprehensive information on the cardiovascular safety profile of VIOXX, you may request the comprehensive PIR. This will be sent via Fed EX within 2 days.
- Transition your discussion to the current strategy and messages for VIOXX®.

Do not proactively discuss any of the recent press stories. Respond to questions by requesting a PIR and in accordance with the obstacle-handling guide.

This information is provided for your background information *only* and is not to be used in discussions with physicians. The following press release was issued in response to an article in Tuesday's New York Times on the cardiovascular effects of VIOXX.

Background Information:

Tuesday May 22, 1:21 pm Eastern Time

Press Release

SOURCE: Merck & Co., Inc.

Merck Confirms Favorable Cardiovascular Safety Profile of Vioxx(R)

UPPER GWYNEDD, Pa., May 22 /PRNewswire/ – In response to news and analyst reports of data the Company first released a year ago, Merck & Co., Inc. today reconfirmed the favorable cardiovascular safety profile of Vioxx® (rofecoxib), its medicine that selectively inhibits COX-2. Vioxx was approved by the Food and Drug Administration in May 1999 for the management of osteoarthritis and the relief of acute pain in adults based on efficacy and safety studies involving nearly 4,000 patients. More than 33 million prescriptions have been written for Vioxx in the United States since its introduction.

The results of the Vioxx Gastrointestinal Research study were first released in March 2000. Since that time, the data have been widely reported, published in The New England Journal of Medicine and discussed extensively by an FDA Advisory Committee.

In VIGOR, Vioxx 50 mg, a dose two-times the highest chronic dose approved for osteoarthritis, significantly reduced the risk of serious GI side effects by half compared to a commonly used dose of naproxen (1,000 mg) in rheumatoid arthritis patients. The Advisory Committee recommended that these results be included in the labeling for Vioxx. Vioxx is not indicated for rheumatoid arthritis.

Although the VIGOR study was a GI outcomes study and was not designed to show differences in cardiovascular effects, significantly fewer heart attacks were observed in patients taking naproxen (0.1 percent) compared to the group taking Vioxx 50 mg (0.5 percent) in this study. There was no difference in cardiovascular mortality between the groups treated with Vioxx or naproxen. Patients taking aspirin did not participate in VIGOR.

In extensive discussions, the Advisory Committee explored this finding, other studies of Vioxx and possible explanations for this result in VIGOR. In the completed osteoarthritis trials and on-going clinical trials with Vioxx 12.5 mg, 25 mg and 50 mg in 30,000 patients, there was no difference in the incidence of cardiovascular events, such as heart attacks, among patients taking Vioxx, other NSAIDs and placebo.

At the Advisory Committee meeting, Merck scientists said the VIGOR finding is consistent with naproxen's ability to block platelet aggregation by inhibiting COX-1 like aspirin, which is used to prevent second cardiac events in patients with a history of heart attack, stroke or other cardiac events. This is the first time this effect of naproxen on cardiovascular events has been observed in a clinical study. Other potential explanations were advanced by the FDA reviewer and were discussed with the Advisory Committee. The Committee recommended that the data on cardiovascular events in VIGOR be included in the labeling for Vioxx.

In addition, the Committee agreed that the prescribing information for both Vioxx and Celebrex® (celecoxib) should reflect the fact that neither of these selective NSAIDs confer cardioprotective benefits and are not a substitute for low-dose aspirin. The Committee also recommended that other studies be conducted to further explore the safety of concomitant use of selective NSAIDs and low-dose aspirin.

In a separate GI outcomes study in osteoarthritis and rheumatoid arthritis patients, celecoxib, another agent that selectively inhibits COX-2, was compared to the NSAIDs diclofenac and ibuprofen. Pharmacia, maker of celecoxib, has indicated that there were no differences among celecoxib, ibuprofen and diclofenac on these cardiovascular events. In Pharmacia's background package submitted to the FDA for the Advisory Committee meeting, the incidence of patients taking celecoxib who experienced a heart attack was cited as 0.5 percent, 0.3 percent among diclofenac patients, and 0.5 percent among patients taking ibuprofen.

Focus:

Remain focused on your efficacy messages for VIOXX. Remember that the primary attribute for physicians and patients is pain relief.

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

No. COX 01-031
May 24, 2001

Bulletin for VIOXX®:
Action Required: REVISED Response to New York Times Article

TO:

All Field Representations with Responsibility for VIOXX	Action Required
All Hospital Representatives	Action Required
A & A Specialty Representatives	Action Required
A & A HSAs	Action Required
Urology Representatives	Action Required
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Managed Care NAEs and Customer Managers (all segments)	Background Information

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PURPOSE:

To provide you with important background information, obstacle responses and faxable PIR instructions in the event that you are questioned by customers about the CV effects of VIOXX.

ACTIONS REQUIRED:

Obstacle Response #38: (originally issued in Bulletin COX 00-029)



"Doctor, there are no head-to-head studies comparing the cardiovascular profile of the two drugs. As a result, you cannot compare the drugs and conclude that one drug had fewer events than the other. What you may be referring to is press reports of the incidence rates in two separate studies. In the VIOXX GI Outcomes Trial (VIGOR), the incidence of MI was 0.5% with VIOXX and 0.1% with naproxen. In a separate GI outcomes trial of Celebrex, the CLASS study, Searle has reported that the incidence of MI was 0.5% with Celebrex, 0.3% with diclofenac, and 0.5% with ibuprofen. Again, doctor, I want to emphasize that the results of two different studies can't be compared, and that's particularly true here when you have studies of differing duration and in different patient populations."

If the doctor asks you further for the incidence of MI from the OA studies presented in the package insert for VIOXX tell them:

"In the clinical OA trials for VIOXX reported in our package insert, the incidence of MI was less than 0.1% with VIOXX."

Use your CV Card to show the data on studies involving VIOXX and various NSAIDs (ibuprofen, diclofenac, and nabumetone) on overall mortality and CV mortality rates

"Doctor, As you can see, Cardiovascular Mortality as reported in over 6,000 patients was VIOXX .1 vs. NSAIDs .8 vs. Placebo 0."

Physician Inquiries:

Reminder: In accordance with policy letters 110, 118, and 131, Field Personnel, including Professional Representatives, HSAs, Hospital Tablet Representatives, Specialty Representatives and NAEs may not discuss off-label information about VIOXX with health care professionals (HCP). In accordance with policy letter 104A, Field Personnel may submit PIRs to Medical Services when an HCP has an unsolicited request for information.

PURPOSE:

To provide you with toll free phone numbers for the one Fax PIR available from Medical Services in response to unsolicited requests for information from HCPs regarding VIOXX and Response to media reports about cardiovascular adverse events.

ACTION REQUIRED:

In response to unsolicited questions from HCPs, you may request PIRs from Medical Services by using EITHER the interactive voice response (IVR) same day fax service, or by using the usual PIR request methods as stated in policy 104A. PIRs requested via the IVR same day fax service will be provided as a "nonpersonalized" Dear Doctor Letter. Specific steps for using the IVR fax service are outlined below.

OVERVIEW:

1. IVR FAX METHOD –

Effective Thursday 5/24 3 pm ET, through close of business Friday, June 29, 2001 (excluding holidays), Medical Services will have one PIR available via fax to respond to the following type of inquiry:

- **Fax = VIOXX and Response to Media Reports about Cardiovascular Adverse Events**

In response to unsolicited questions about the above topics, the PIR – **VIOXX and Response to Media Reports about Cardiovascular Adverse Events** will be available from Medical Services via the interactive voice response (IVR) same day fax service and provided as a "nonpersonalized" Dear Doctor Letter.

Toll Free Fax PIR Request Telephone Number:

You may submit a HCPs request for a faxed PIR(s) by simply calling 1-877-372-7064.

- This toll free phone number will be made available from 8:00am – 10:00pm (ET). Since this line is an IVR system, a touch tone phone must be used in order to provide the pertinent information needed as prompted in the system.

Please follow the detailed instructions outlined below for requesting the faxable "nonpersonalized" Dear Doctor Letter.

You should be prepared to provide the following pertinent information as prompted by the system:

- Your Region, District, and Territory identifier
- Requesting Physician's 5 digit ZIP code
- Requesting Physician's full name and professional degree (speak)
- Requesting Physician's full mailing U.S. address (speak)
- Requesting Physician's phone number with area code
- Requesting Physician's FAX number with area code

Select the faxes requested by the physician:

- **FAX = VIOXX and Response to Media Reports about Cardiovascular Adverse Events**

IMPORTANT NOTE: PIRs ARE NOT TO BE REPRODUCED IN ANY FORM!

This one fax will be sent directly to the requesting physician's office as "nonpersonalized" Dear Doctor Letter. This fax should arrive as soon as 15 minutes from the time of the request. You must leave a copy of the circular for VIOXX with the HCP. (Note: For pharmacists, nurses, and physician assistants, you may also want to send the 'Dear Doctor' letter.)

You also have the option to follow the usual procedure established for processing a PIR using the methods through Medical Services as stated in Policy 104A.

Toll Free IVR HELPLINE Telephone Number:

If you experience difficulty with the IVR system or if there is difficulty receiving the fax, representatives should call the IVR HELPLINE at 1-888-721-7204 (9:00 am to 7:00 pm ET)

- This number will be on the cover sheet of both faxes available to the physician.
- This number is staffed from 9:00 am to 7:00 pm ET.

2. ADDITIONAL OTHER PIRS FOR VIOXX ARE AVAILABLE FROM MEDICAL SERVICES IN RESPONSE TO UNSOLICITED INQUIRIES FROM HCPs BY USING THE USUAL METHODS TO SUBMIT PIRS AS STATED IN POLICY LETTER 104A.

The usual PIR request methods are (note: choose only one method for each request):

- INSIGHT and processing using the PIR screen;
- PIR hotline at 800-MERCK66 (8:30 am to 6:30 pm ET as extended hours) in Medical Services. This phone number is NOT to be given to an HCP, but is for Merck Field Personnel use only to verbally submit the questions asked by HCPs. PIR inquiries may be submitted to Medical Services 24 hours a day, 7 days a week with voice message available after hours (6:30pm to 8:30am ET).
- Faxing your request to Medical Services at 800-MERCK68.

If a health care provider requests to speak with a Merck health care professional, the Merck National Service Center should be called at 800-NSCMERCK (business hours of 8:00 am to 7:00 pm ET; For emergency issues, Medical Services after-hours Call Coverage is 24 hours a day/ 7 days a week.)

Remember to always provide a balanced discussion consistent with the health care provider's knowledge of the product and the product prescribing information. Please continue to provide competitive and promotional feedback to the National Service Center (NSC). The NSC is staffed Monday through Friday, 8:00am to 7:00pm Eastern Time. Please contact the NSC at 1-800-NSC-MERCK or 1-800-672-6372.

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

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