

No. COX 03-080
Sep 17, 2003

Bulletin for VIOXX:

Upcoming Abstracts for VIOXX at the 2003 American College of Rheumatology meeting and Obstacle Response for Observational Analysis by Solomon, et. al.

TO:

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| Office Based Representatives with Responsibility for VIOXX | Action Required |
| A & A Specialty Representatives | Action Required |
| A & A HSAs | Action Required |
| Hospital Representatives with Responsibility for VIOXX | Action Required |
| Neurology Specialty Representatives | Action Required |
| CV Specialty Representatives | Action Required |
| Urology Specialty Representatives | Action Required |
| HIV Specialty Representatives | Action Required |
| NAEs and Customer Managers (all segments) | Action Required |
| Regional Medical Directors | General Information |

DO NOT INITIATE DISCUSSIONS ON ANY OF THE UPCOMING ABSTRACTS ON VIOXX THAT WILL BE PRESENTED AT THIS YEAR'S AMERICAN COLLEGE OF RHEUMATOLOGY MEETING. YOU MAY RESPOND TO CUSTOMER INQUIRIES ONLY AS SPECIFICALLY SET FORTH IN THIS BULLETIN. IF A PHYSICIAN HAS ADDITIONAL QUESTIONS THAT CANNOT BE ANSWERED AS SET FORTH IN THIS BULLETIN, OFFER TO SUBMIT A PIR.

PURPOSE:

To provide you with the titles of some of upcoming abstracts for VIOXX that will be presented at the 2003 American College of Rheumatology meeting. Also, to provide you with internal information and an obstacle response for the abstract entitled, "The Relationship between Selective COX-2 Inhibitors and Acute Myocardial Infarction," by Daniel H. Solomon et al., which was co-sponsored by Harvard and Merck, in the event you are questioned by your customers.

OVERVIEW:

2003 ACR ABSTRACTS for ROFECOXIB (for your information)



2003 ACR Abstracts
for rofecoxib

ACTIONS REQUIRED:

- We are providing this for your background information only
- Do not initiate discussions on any of the upcoming abstracts with physicians
- Use the following obstacle response when asked an **unsolicited** question by a physician regarding the abstract by Solomon, et. al.
- If a physician raises additional questions about the Solomon abstract **OR** questions about any **other** abstract presented at ACR, you may submit a PIR
- Return to your efficacy messages for VIOXX based upon your physician's beliefs after addressing the obstacle
- Do not deviate from the language in this obstacle response
- Remember to provide appropriate balancing information as part of all product discussions



OBSTACLE RESPONSES:

Titulars in abstract of ACP that shows VIOXX causes more CV events than Celecoxib

1. Merck stands behind the overall safety of VIOXX

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.

2. Interpret with caution

Merck believes that conclusions from retrospective, observational analyses should be interpreted with caution. These types of analyses are variable in the study design and patient populations and have a number of limitations, including: prescribing that is not consistent with product labels, potential uncontrolled confounding of CV risk factors, no OTC drug data (e.g. aspirin use), limited endpoint verification, and unknown compliance with therapy. Prospective, randomized, controlled clinical trials are the gold standard.

3. Review Precautions Section of Label for VIOXX GI Outcomes Research Study

Doctor, let me review the cardiovascular effects section of the VIOXX label.

- In the VIOXX GI Outcomes Research Study, 8076 patients (mean age 58) were followed for an average of 9 months.
- Cardiovascular thrombotic events were 45 for VIOXX 50mg qd as compared to 19 for naproxen 500mg bid.
- Mortality due to cardiovascular thrombotic events (7 vs 6, VIOXX vs naproxen respectively) was similar between the treatment groups.

4. Review Precautions Section of Label for Placebo-Controlled Trials

Doctor, also contained in the cardiovascular effects section of the label for VIOXX is data from placebo-controlled trials. Let me review that data with you.

- 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.
- Serious cardiovascular thrombotic events were 21 vs 35 for patients treated with VIOXX 25mg qd vs placebo, respectively.
- Mortality due to cardiovascular thrombotic events was 8 vs 3 for VIOXX vs placebo, respectively.

5. Significance Unknown

As stated here in the label, the significance of the cardiovascular findings from these 3 studies is unknown and prospective studies specifically designed to compare the incidence of serious CV events in patients taking VIOXX vs NSAID comparators or placebo have not been performed.

6. VIOXX is not a replacement for aspirin

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.

7. PIR

If the physician continues to have questions about the Solomon analysis, submit a PIR.



Understand and Interpret the Study Data as Presented at ADR showing VIOXX causes more CV events than Celebrex

1. Merck supports many types of studies

Merck supports many scientific endeavors, including at times, observational analyses as part of our overall contribution to science. Merck takes many different approaches in analyzing its products, including randomized, controlled clinical trials (the gold standard) and retrospective observational analyses.

2. Interpret with caution

It is important to note that Merck believes results from retrospective, observational analyses should be interpreted with caution. Clinical decisions should be made based on large, randomized, placebo-controlled studies. It is important to consider any observational analysis within the context of data from the large, randomized, controlled clinical trials of VIOXX

3. Merck stands behind the overall safety of VIOXX

Doctor, based on all of the data that are available, Merck stands behind the overall efficacy and safety profile of VIOXX

4. Solomon response or PIR

If the physician continues to have questions about the Solomon analysis, you may discuss the clinical data using the approved obstacle response ("*There is an abstract at ACR that shows VIOXX causes more CV events than Celebrex*") or submit a PIR.

Resume core messages for VIOXX

Deliver your **Core Messages for VIOXX** based on physician beliefs



*** Slip Sheet ***

Child

ABSTRACT INFORMATION:

Internal Information Only – Not to be discussed with or shown to physicians or customers

Solomon, et al

Title: The Relationship Between Selective COX-2 Inhibitors and Acute Myocardial Infarction

Publication: ACR abstract

Support: Brigham Women's Hospital, Boston, MA and Merck & Co., Inc. (through an Blue Bell, PA

Author: Daniel H Solomon, Sebastian Schneeweiss, Robert J Glynn, Yuka Kiyota, Raisa Levin, Helen Mogun, Carolyn C. Cannuscio, Jerry Avorn

Design: A retrospective, matched case-control study of 54,475 patients > 65 years of age who received their medications through two state-sponsored pharmaceutical benefits programs in the US. All health care utilization encounters were examined to identify hospitalizations for AMI. A regression analysis was used to assess the relative risk of AMI in patients who took rofecoxib compared with persons taking celecoxib, no NSAID, or nonselective NSAIDs.

Results: Current use of rofecoxib was associated with an increased adjusted relative risk of AMI compared with celecoxib and with no NSAID. There was a trend that was elevated in dose-specific comparisons. (Doses of rofecoxib >25mg were associated with the highest risk). In analyses of new users of coxibs, the adjusted relative risk of AMI associated with use of rofecoxib compared to celecoxib was higher in the first 90 days. This elevation in risk was seen in persons taking both dosage levels of rofecoxib.

Conclusion: In this observational study, current rofecoxib use was associated with an increased adjusted relative risk of acute myocardial infarction compared with celecoxib use and with no NSAID use. Dosages of rofecoxib > 25 milligrams were associated with the highest risk. Risk may be highest in the first 90 days.

PIR Instructions

Reminder: In accordance with policy letters 110, 118, and 131, Field Personnel, including Professional Representatives, HSAs, Hospital Representatives, Specialty Representatives and NAEs may not discuss or respond to questions about off-label information about VIOXX. In accordance with policy letter 104A, Field Personnel may submit PIRs to Medical Services only when a Health Care Professional has an **unsolicited** request for such information. You must not prompt or solicit any questions or requests for off-label information.

FASTER DELIVERY OF PIRs

In an effort to provide enhanced customer service, Medical Services has added additional functionality that will permit PIR responses to be Emailed or Faxed to Health Care Professionals.

In order to request one of these forms of delivery, two new topics have been added in Insight under the "TOPICS" tab:

GEN – Respond to this PIR by Email

GEN – Respond to this PIR by FAX

To request that a PIR be sent via Email or Fax, simply choose the appropriate method of delivery when submitting the PIR request. If neither of these methods of delivery is chosen, the PIR will automatically be sent to the health care professional via regular mail. If requesting that the PIR be sent via Email or Fax, only one title or question may be submitted with the PIR. Before requesting



a PIR, please discuss how the customer would like the PIR delivered (mail, Email, or Fax). You must obtain permission from healthcare professionals to send a PIR via Email or FAX. If the PIR is to be sent via Email or Fax, please make sure that you obtain a valid Email address or Fax number, and confirm that the information is correct in Insight. Please obtain a phone number as well in case there is a problem sending the Email or Fax.

Requests for Emailing or Faxing of PIRs can still be made through the 1-800-MERCK66 request line. This service is not available for HSAs or NAEs. Please see GEN03-051 for additional information.

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



a PIR, please discuss how the customer would like the PIR delivered (mail, Email, or Fax). You must obtain permission from healthcare professionals to send a PIR via Email or FAX. If the PIR is to be sent via Email or Fax, please make sure that you obtain a valid Email address or Fax number, and confirm that the information is correct in Insight. Please obtain a phone number as well in case there is a problem sending the Email or Fax.

Requests for Emailing or Faxing of PIRs can still be made through the 1-800-MERCK66 request line. This service is not available for HSAs or NAEs. Please see GEN03-051 for additional information.

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1-800-NSC MERCK (1-800-672-6372).**



Other abstracts on rofecoxib

Induction of Apoptosis by Rofecoxib, a Specific Cyclooxygenase-2 Inhibitor, in Peripheral Blood Mononuclear Cells from Rheumatoid Arthritis Patients, Maria C. Muñoz-Villanueva, Rafael Ramirez-Chamond, Eduardo Collantes-Estevez. Hospital Universitario Reina Sofia, Córdoba, Spain

The Relationship Between COX-2 Specific Inhibitors and Hypertension, Daniel H. Solomon¹, Sebastian Schneeweiss², Raisa Levin², Jerry Avorn². ¹Division of Pharmacoepidemiology, Division of Rheumatology, Brigham and Women's Hospital, Boston, MA; ²Division of Pharmacoepidemiology, Brigham and Women's Hospital, Boston, MA

Predictors of Aspirin Co-prescription Among NSAID and COX-2 Inhibitor Users with Cardiovascular Risk Factors, J. D. Greenberg¹, C. O. Bingham¹, S. B. Abramson¹, G. Reed², J. Kremer for the CORRONA Database³. ¹NYU-Hospital for Joint Diseases, New York, NY; ²U. Massachusetts, Worcester, MA; ³Center for Rheumatology, Albany, NY

A Double-Blind, Placebo-Controlled, Randomized 2-Week Study of Valdecoxib 10 mg QD and Rofecoxib 25 mg QD in Relieving the Signs and Symptoms of Osteoarthritis of the Knee in Flare, Roland W. Moskowitz¹, Gail Cawkwell². ¹Case Western Reserve University School of Medicine and University Hospitals of Cleveland, Cleveland, OH; ²Pfizer Inc, New York, NY

Lumiracoxib, a Novel Cyclooxygenase-2 Selective Inhibitor, has Improved Gastrointestinal Safety and Tolerability Compared with Non-selective Nonsteroidal Anti-inflammatory Drugs: a Pooled Analysis, C. Hawkey¹, G. Hoexter², D. Richard², X. Gitton², W. Weinstein³. ¹University Hospital, Nottingham, United Kingdom; ²Novartis Pharma AG, Basel, Switzerland; ³David Geffen School of Medicine at UCLA, Los Angeles, CA

Is Acetaminophen Truly Safe and Effective in OA of the Hip and Knee? A Best Evidence Synthesis, Jag Mangru, Suresh Kumar, Paul M. Peloso. University of Iowa Health Care, Iowa City, IA

Selective COX-2 Inhibitor Use and Myocardial Infarction: Assessment of Potential Confounding Bias, Sebastian Schneeweiss¹, Elisabeth H. Tsai¹, Robert J. Glynn¹, Jerry Avorn¹, Daniel H. Solomon². ¹Division of Pharmacoepidemiology, Brigham and Women's Hospital, Boston, MA; ²Division of Pharmacoepidemiology, Division of Rheumatology, Brigham and Women's Hospital, Boston, MA

Selective Cyclooxygenase-2 (COX-2) Inhibitors Protect Against Breast Cancer, Elham Rahme, Kaberi Dasgupta, Joumana Ghosn, Louise Pilote, Marie Hudson. McGill University, Montreal, PQ, Canada

Gastrointestinal Effects of Rofecoxib and Celecoxib versus Acetaminophen among Patients on Low Dose Aspirin, E. Rahme¹, M. Bardou², Y. Toubouti¹, A. N. Barkun¹. ¹Montreal General Hospital, Montreal, PQ, Canada; ²Clinical Pharmacology Unit, Dijon, France

Analgesic Efficacy of Lumiracoxib Compared with Placebo, Rofecoxib and Celecoxib in Patients with Postoperative Dental Pain, D. Kellstein¹, J. Fricke, Jr.², D. Ott¹, S. Jayawardene¹. ¹Novartis Pharmaceuticals Corporation, East Hanover, NJ; ²PPD Development, Austin, TX

Not to be shown to physicians, for use by Merck Representatives only
Remember to provide appropriate balancing information as part of all product discussions.



Effect of LAS34475, a New Selective COX-2 Inhibitor, in Two Animal Models of Arthritis, Mercè Amat, Neus Prats, Francisco J. Caturla, María I. Crespo, Hamish Ryder, Jorge Beleta, Nuria Godessart. Almirall Research Center, Barcelona, Spain

Prophylactic Effect of a Coxib in Acute Monosodium Urate (MSU) Crystal Induced Inflammation in a Rat Subcutaneous Air Pouch, H. Ralph Schumacher, Selim Nalbant, Lan Chen, Marie S. Sieck, Gilda Clayburne. University of PA, VA Med. Ctr, Philadelphia, PA

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