



**VIOXX TIMELINE Key Dates for VIGOR and Long-term, Placebo-controlled Studies Implemented to Provide Cardiovascular Safety Data**

<b><u>1993</u></b>	Studies published in which indobufen (Circulation, 1993, 87:162-164) and the non-selective NSAID flurbiprofen (European Heart Journal, 1993, 13, 951-957) are shown to reduce cardiovascular (cv) events.
<b><u>1998</u></b>	
April	Results of FitzGerald study first presented. Among the results of the study was the surprising discovery that COX-2 specific inhibitors reduced the urinary excretion of prostacyclin metabolite. Based on these results, it was, for the first time, hypothesized that COX-2 specific inhibitors may alter the balance between prostacyclin and thromboxane and thereby increase the risk of cv events.
	Trial of VIOXX versus placebo in the prevention of Alzheimer's in patients with Mild Cognitive Impairment (MCI) begins.
Nov	Vioxx New Drug Application (NDA) submitted to the U.S. Food & Drug Administration (FDA). The application included data on approximately 5,400 osteoarthritis patients who participated in 8 double-blind, placebo-controlled and active-comparator studies. In these studies, similar rates of investigator-reported thrombotic cardiovascular adverse events were seen with VIOXX, placebo, and comparator NSAIDs (ibuprofen, diclofenac, or nabumetone).
<b><u>1999</u></b>	
Jan	VIOXX Gastrointestinal Outcomes Research <sup>1</sup> (VIGOR) trial initiated.
Feb	First trial of VIOXX versus placebo for the treatment of Alzheimer's disease begins.
April	Public meeting of FDA Advisory Committee on VIOXX NDA.
May	VIOXX approved by the FDA.
Oct	Adenomatous Polyp Prevention On VIOXX <sup>2</sup> (APPROVe) trial protocol finalized.

## 2000

Feb APPROVe trial enrollment begins.

March Preliminary results from VIGOR become available to Merck.

March Merck unblinded to safety data from two ongoing Alzheimer's studies – one for prevention and one for treatment – that compare VIOXX to placebo. These data did not show a difference in cardiovascular event rates between VIOXX and placebo.

March Preliminary VIGOR results submitted to the FDA.

March News release on preliminary results of VIGOR issued by Merck.

April Second trial of VIOXX versus placebo for the treatment of Alzheimer's begins.

May VIGOR analysis based upon the prespecified cutoff dates submitted to the *New England Journal of Medicine* for publication.

May VIGOR presented at Digestive Disease Week.

June VIGOR analysis based upon the prespecified cutoff dates submitted to FDA in a Supplemental New Drug Application, which included draft prescribing information.

Oct Final VIGOR data submitted to FDA in a Safety Update Report.

Nov The GI and cardiovascular safety findings from VIGOR published in *The New England Journal of Medicine*.

First VIOXX versus placebo trial in the treatment of Alzheimer's disease ends.

In preparation for VIGOR Advisory Committee, second interim analysis of safety data from Alzheimer's prevention and treatment trials conducted, and again did not show a difference in cardiovascular event rates between VIOXX and placebo.

## 2001

Feb Public meeting of FDA Advisory Committee on VIGOR.

May Second trial of VIOXX versus placebo for treatment of Alzheimer's disease stopped.

Oct Pooled analysis of cardiovascular data from 28,000 patients in 23 studies published in *Circulation*. Analysis demonstrated that VIOXX was not associated with excess cardiovascular thrombotic events compared with either placebo or non-naproxen NSAIDs.

Sept Merck and Oxford University sign letter of intent to conduct the VIOXX in Colorectal Cancer Therapy: definition of Optimal Therapy<sup>3</sup> (VICTOR) trial.

Nov APPROVe enrollment completed.

## 2002

April U.S. Prescribing Information for VIOXX updated with VIGOR

information and data from two placebo-controlled studies  
April First patient is enrolled in VICTOR trial.  
June Pooled analysis of placebo-controlled studies in patients with Alzheimer's and MCI presented at EULAR. The incidence of serious cardiovascular adverse events in this population was similar on VIOXX and placebo.

### **2003**

March VIOXX in Prostate cancer (ViP) trial protocol finalized.  
April Trial of VIOXX versus placebo in MCI ends.  
June ViP trial enrollment begins.  
Updated pooled analysis of Alzheimer's treatment and MCI data presented at EULAR. The cardiovascular event rate in patients taking VIOXX 25 mg continued to be similar to the rate in patients taking placebo; mean duration of treatment was 1.2 years in VIOXX group and 1.3 years in placebo group.  
Oct Updated pooled analysis published in the American Heart Journal. Analysis demonstrated that VIOXX was not associated with excess cv thrombotic events compared with either placebo or non-naproxen NSAIDs.

### **2004**

Sept APPROVe External Data Safety Monitoring Board notifies Merck of its recommendation to end APPROVe trial.  
Sept APPROVe, ViP and VICTOR trials terminated early.  
Sept Merck voluntarily withdraws VIOXX from the market.  
Nov APPROVe trial scheduled to end.

### **2005**

Aug ViP trial enrollment scheduled to be completed.

### **2011**

Aug ViP trial scheduled to end.

<sup>1</sup> In VIGOR, Vioxx 50 mg once daily (n=4,047) – a dose twice the highest recommended chronic dose -- was compared to a common therapeutic dose of naproxen 500 mg twice daily (n=4,029) in patients with rheumatoid arthritis (median length of participation was nine months). The study assessed the incidence of serious GI events and the most serious, or "complicated," GI events, which included perforations, obstructions or major bleeding (PUB) in the upper GI tract. The study was designed to exclude patients requiring aspirin for cardioprotection.

In VIGOR, Vioxx 50 mg once daily significantly reduced the risk of serious GI events by 54 percent and the risk of complicated GI events by 57 percent compared to naproxen 500 mg twice daily. A total of 56 patients treated with Vioxx experienced a serious GI

event compared to 121 patients taking naproxen, and a total of 16 patients receiving Vioxx had a complicated GI event versus 37 patients taking naproxen. In the study, the reduction in risk for serious and complicated GI events with Vioxx was maintained in patients both at high risk for developing a PUB and in patients without risk factors. Such risk factors include: prior history of a PUB, age of 65 or older, *Helicobacter pylori* infection or concomitant use of corticosteroids.

In VIGOR, a statistically significant higher incidence of serious cardiovascular thrombotic events was seen in patients receiving Vioxx 50 mg once daily compared to patients treated with naproxen 500 mg twice daily. A total of 45 serious cardiovascular thrombotic events occurred among 4,047 patients taking Vioxx compared to 19 among 4,029 taking naproxen. This was largely due to a difference in the incidence of non-fatal heart attacks: 18 for Vioxx and 4 for naproxen. The number of cardiovascular thrombotic deaths was similar in patients treated with Vioxx (n=7) compared to naproxen (n=6).

<sup>2</sup> APPROVe was a multi-center, randomized, placebo-controlled, double-blind study to determine the effect of 156 weeks (3 years) of treatment with rofecoxib on the recurrence of adenomatous polyps of the large bowel in patients with a history of colorectal adenomas. The study included approximately 2600 patients aged 40-96; approximately 62% male. Aspirin was allowed in the study.

In APPROVe there was an increased relative risk for confirmed cardiovascular events, such as heart attack and stroke, beginning after 18 months of treatment for patients taking VIOXX as compared to placebo. Results for the first 18 months of the study did not show an increased risk of confirmed CV events on VIOXX and in this respect, the results are similar to the results of two prior placebo controlled studies described in the current U.S. labeling for VIOXX.

Merck followed the recommendation of the study's External Safety Monitoring Board and terminated this trial on September 30, 2004.

<sup>3</sup> VICTOR was a randomized, double-blind, placebo-controlled, international, multicenter study of VIOXX in 7,000 colorectal cancer patients following potentially curative therapy. The primary hypothesis tested in the study was that VIOXX administered for two years will result in greater overall survival compared with placebo. CV events were monitored by the VICTOR trial investigators and Merck as part of the adverse events monitoring conducted as part of the study. The study was stopped on September 30, 2004.

<sup>4</sup> ViP was a randomized, double-blind, placebo-controlled, multicenter study to evaluate the effects of VIOXX in decreasing the risk of prostate cancer. The study protocol called for 15,000 male patients, aged = 50 and = 75 years, with a life expectancy of greater than 6 years, with PSA = 2.5 ng/mL and = 10 ng/mL to be enrolled. The primary hypothesis to be tested in the study was that the risk of developing prostate cancer over six years of treatment will be lower in patients treated with VIOXX 25 mg/day than in patients treated with placebo; and that treatment with VIOXX would be generally safe and well tolerated. An external safety monitoring board was in place to monitor cardiovascular adverse events

as part of this study. The trial was halted on September 30, 2004.

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#### **Forward-Looking Statement**

This document contains "forward-looking statements" as that term is defined in the Private Securities Litigation Reform Act of 1995. These statements involve risks and uncertainties, which may cause results to differ materially from those set forth in the statements. The forward-looking statements may include statements regarding product development, product potential or financial performance. No forward-looking statement can be guaranteed, and actual results may differ materially from those projected. Merck undertakes no obligation to publicly update any forward-looking statement, whether as a result of new information, future events, or otherwise. Forward-looking statements in this press release should be evaluated together with the many uncertainties that affect Merck's business, particularly those mentioned in the cautionary statements in Item 1 of Merck's Form 10-K for the year ended Dec. 31, 2003, and in its periodic reports on Form 10-Q and Form 8-K (if any) which the company incorporates by reference.