

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

<u>1993</u>	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.
<u>1998</u>	
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).
<u>1999</u>	
Jan	VIOXX Gastrointestinal Outcomes Research ¹ (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 ² (APPROVe) trial protocol finalized.

2000

Feb APPROVe trial enrollment begins.

March Preliminary results from VIGOR become available to Merck.

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

March Preliminary VIGOR results submitted to the FDA.

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 show no difference in cardiovascular event rates between VIOXX and placebo.

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

May Preliminary VIGOR data submitted to the *New England Journal of Medicine* for publication.

May VIGOR presented at Digestive Disease Week.

June Final VIGOR data submitted to FDA in a Supplemental New Drug Application, which included draft prescribing information.

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, again showing no 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 Alzheimer's disease stopped.

Oct Pooled analysis of cardiovascular data from Phase II/III 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 Therapy³ (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.

¹. 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).

² 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.

³ 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.

⁴ 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. Cardiovascular adverse events were monitored by an external safety monitoring board as a part of the study. The trial was halted on September 30, 2004.

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