

MEMO to file  
January 28, 2004  
IND 46,894  
NDA 21-042/21-052 - Vioxx

From: Lourdes Villalba, MD, Medical Officer, DAAODP (HFD-550)  
To: Brian Harvey, MD, Acting Division Director, DAAODP  
Through: Sharon Hertz, MD, Deputy Division Director, DAAODP

Re: IND 46,894, SN A80 (submitted December 17, 2003). Response to FDA request for information for Studies 078 and 091 (Alzheimer's studies), requested by the Division in December 9, 2002. Cross-reference IND 55,269 (DNDP, HFD-120).

### 1. Background

In view of the cardiovascular findings in VIGOR, the FDA conducted a detailed review of all available data on cardiovascular thrombotic events in a placebo-controlled database of approximately 3,000 patients enrolled in three studies (078, 026 and 091) for the prevention of Alzheimer's disease (AD). These studies were not designed to evaluate cardiovascular outcomes. Patients at high cardiovascular risk such as those with a recent history of myocardial infarction and stroke, and patients taking estrogen replacement therapy were excluded; duration of the studies was shorter than most CV studies. After enrollment was complete, patients identified as potential candidates for cardiovascular prophylaxis were started on low dose aspirin (approximately 6% of patients in each treatment arm). (A full description of the studies is in the MO review of the Complete Response to the Approvable letter of April 6, 2001, dated November 28, 2001.)

Despite all of the above, these studies included an elderly population (mean age 75 years) and provided a relatively large placebo-controlled database (rofecoxib N= 1267, placebo N= 1464), with a median exposure of 14 months with a substantial number of MI and cerebrovascular events for analysis. Therefore, data from two of these studies -one completed (091) and one ongoing (078) at the time of labeling - were included in the Vioxx label, along with the VIGOR cardiovascular data. (Study 026 had been terminated early and had short exposure, therefore was not included in the analysis).

The Vioxx label currently carries the following section:

#### *Cardiovascular Effects*

The information below should be taken into consideration and caution should be exercised when VIOXX is used in patients with a medical history of ischemic heart disease.

In VIGOR, a study in 8076 patients (mean age 58; VIOXX n=4047, naproxen n=4029) with a median duration of exposure of 9 months, the risk of developing a serious cardiovascular thrombotic event was significantly higher in patients treated with VIOXX 50 mg once daily (n=45) as compared to patients treated with naproxen 500 mg twice daily (n=19). In VIGOR, mortality due to cardiovascular thrombotic events (7 vs 6, VIOXX vs naproxen, respectively) was similar between

the treatment groups. (See CLINICAL STUDIES, *Special Studies, VIGOR, Other Safety Findings: Cardiovascular Safety.*) In a placebo-controlled database derived from 2 studies with a total of 2142 elderly patients (mean age 75; VIOXX n=1067, placebo n=1075) with a median duration of exposure of approximately 14 months, the number of patients with **serious cardiovascular thrombotic events** was **21 vs 35** for patients treated with VIOXX 25 mg once daily versus placebo, respectively. In these same 2 placebo-controlled studies, **mortality due to cardiovascular thrombotic events** was **8 vs 3** for VIOXX versus placebo, respectively. The significance of the cardiovascular findings from these 3 studies (VIGOR and 2 placebo-controlled studies) is unknown. Prospective studies specifically designed to compare the incidence of serious CV events in patients taking VIOXX versus NSAID comparators or placebo have not been performed.

In December 2002, at the time of termination of study 078, the Division asked the Sponsor to provide follow up information from the combined studies 091 and 078, to update the label.

## 2. Review of the current submission:

The current submission includes specific safety analyses from combined studies 078 and 091 requested by DAAOPD in December 2002, as well as the complete report for study 078. The safety data consist of listings, tables and analysis of deaths, serious adverse events, discontinuations due to adverse events, cardiovascular thrombotic events and hypertension-related events. There are no narratives or case report forms. The Sponsor is planning to submit a labeling supplement including both studies by the end of March 2004.

The cutoff date for the numbers of serious CV/T events in the label was March, 2002. The current numbers are as follows:

	Rofecoxib	Placebo	
Serious CVT events in study 078	38	36	
Study 091	4	12	
<b>Combined</b>	<b>42</b>	<b>48</b>	(RR approx 1 but increases with time Is >1.5 after 18 months)
<b>MI combined</b>	<b>22</b>	<b>20</b>	
Mortality for CVT events 078	8	4	
091	3	1	
<b>Combined</b>	<b>11</b>	<b>5</b>	overall RR= 2.5
Additionally, all cause mortality			
078	27	15	
091	14	8	
<b>Combined</b>	<b>41</b>	<b>23</b>	overall RR= 2.2 (it changes with time, maximum RR between 6-12 months = 17.4)

There is no excess of MI in the rofecoxib 25 mg group, as compared to placebo (22 vs 20, respectively), but consistent with the prior analysis, there is higher all-cause mortality and cardiovascular mortality in patients taking rofecoxib as compared to placebo.

The crude rate for all-cause mortality was 3.8% with Vioxx vs. 2.1% with placebo (p=0.022 by Fisher's test). Patient year adjusted incidence rate was 2.44 and 1.18 per 100 patient-years, respectively. Overall relative risk from the Cox model was 2.23 with 95% CI (1.33, 3.73). As per Table 11 of the Sponsor's submission, there were more "cardiac disorders" (13 vs 7), "infections and infestations" (6 vs 0) and "injury, poisoning and procedural complications" (5 vs 0) in the Vioxx group as compared to placebo. Deaths among the Vioxx treated group included one case of duodenal hemorrhage and one of gastric perforation. No such events occurred in the placebo group.

*The cardiovascular section of the label should be updated to reflect the final number of CV/T events, CV/T deaths and all-cause mortality.*

### **3. Recommendation for regulatory action:**

Information on all cause mortality, CV/T mortality and CV/T events from the combined studies 078 and 091 should appear in the VIOXX label.

The Sponsor is planning to submit a labeling supplemental NDA in March 2004 to include cardiovascular safety data. At that time, full review of the data will be conducted and language will be crafted accordingly.

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