

Memo to file (3/12/02)
 NDA 21-042/s007. VIOXX (rofecoxib).
 Addendum

To: Lawrence Goldkind, M.D., Deputy Division Director, DAAODP
 Through: James Witter, M.D., Ph. D., Team Leader, DAAODP
 From: Maria Lourdes Villalba, M.D., Medical Officer

Re: Cardiovascular data in Alzheimer’s studies

1) Background

In view of the cardiovascular findings in VIGOR, the FDA has been conducting 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 for the prevention of Alzheimer’s disease.

The Alzheimer’s studies were not designed to evaluate cardiovascular outcomes. However, the studies included an elderly population (mean age 75 years). 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). For a description of the studies the reader is referred to this MO review of the Complete Response to the Approvable letter of April 6, 2001, dated November 28, 2001. At the time of the safety update report (SUR) (July 2001) one study has been completed and analyzed (091), one has been terminated early (126) – due to lack of efficacy in study 091 - and one is still ongoing (078). The cut-off date used for these analyses was March 2001. Exposure data are presented in Table 1.

2) Exposure data

Table 1. Alzheimer’s studies. Exposure up to March 16, 2001.

	Rofecoxib 25 mg			Placebo		
	N	Pt/years at risk	Median duration (days)	N	Pt/years at risk	Median duration (days)
<i>091(completed)</i>	346	301	366	346	366	448
<i>078 (ongoing)</i>	721	996	520	729	1098	577
<i>126 (terminated)</i>	381	165	153	376	169	158.5
<i>Total</i>	1448	1461	355.5	1451	1634	421

Source: sponsor’s tables. SUR and 2/29/02 response to request for information.

Reviewer’s comment: exposure to rofecoxib was somewhat shorter as compared to placebo, particularly in studies 091 and 078.

3) Safety results: Deaths and cardiovascular events. (For review of other AE’s the reader is referred to this MO review of the Complete Response to the Approvable letter of April 6, 2001, dated November 28, 2001).

1. Deaths

1.1 Total cause mortality

There were 33 and 20 deaths for all causes in the rofecoxib 25 and placebo groups respectively. If we consider the deaths from the long-term studies only (078 and 091), there were 29 and 15 deaths in the rofecoxib 25 mg and placebo group, respectively. Review of the causes of death did not suggest a particular pattern, with the possible exception of cardiovascular deaths, as noted below. (For a listing of causes of death the reader is referred to the MO review of 11/28/01.)

1.2 Cardiovascular deaths

Of all deaths, 10 and 6 were cardiovascular deaths (See Table 2) in the rofecoxib and placebo groups, respectively. CV deaths include sudden death, fatal MI or stroke – ischemic or hemorrhagic- and ruptured aortic aneurysm

Of the CV deaths, 8 and 4 were adjudicated as cardiovascular thrombotic deaths (by the CV adjudication committee) in the rofecoxib and placebo groups, respectively. By the time study 126 was terminated, there were 4 deaths for all causes in each treatment group. Only one was cardiovascular thrombotic (a fatal MI in a patient who had meningitis in the placebo group.)

Table 2. Listing of Cardiovascular Mortality in Alzheimer’s Studies.

Rofecoxib (n=10)	Placebo (n= 6)
Protocol 091	
332: acute MI (fatal)	784: sudden cardiac death
601: sudden cardiac death	*827 hemorrhagic stroke (fatal)
831: ischemic cerebrovascular stroke (fatal)	* 956 ruptured aortic aneurysm
Protocol 078	
248: sudden cardiac death	1256: sudden cardiac death
359: sudden cardiac death	1378: sudden cardiac death
737: sudden cardiac death	
799: sudden cardiac death	
1025: acute MI (fatal)	
Protocol 126	
*532: hemorrhagic stroke (fatal)	661: acute MI (fatal)
*43: hemorrhagic stroke (fatal)	

* Hemorrhagic events were not “adjudicated” cardiovascular thrombotic events.

Reviewer’s comment: although the numbers are small, the trend suggests more cardiovascular thrombotic deaths in the rofecoxib 25 mg daily group, as compared to placebo (8 vs. 4).

2. Serious Cardiovascular Thrombotic events (fatal and non-fatal)

The three studies included 156 cases of investigator reported serious CV thrombotic events referred for further evaluation by the CV adjudication committee. (Actually, these included cardiovascular cases within a list of pre-specified terms used by the sponsor in prior studies, as well as all deaths – cardiovascular and non-cardiovascular-).

Dr. Shari Targum, from the Division of Cardio-renal products (HFD-110) has conducted a blinded review of adjudication packages for all non-neurologic events referred for adjudication. There was no excess of CV thrombotic events – in particular no excess of myocardial infarction – in the rofecoxib group, upon her review of the data. (See review of December 2, 2001). The division of Neuropharm products (HFD-120) is conducting a similar, blinded review of cerebrovascular events, also in a blinded fashion.

Of note, twenty-two patients had non-neurologic, potential cardiovascular thrombotic events referred for adjudication, for which hospital or nursing home records were either not available or insufficient to adjudicate. Of those, 18 were receiving rofecoxib and 4 were receiving placebo. (Review of cerebrovascular events under review may reveal additional cases with insufficient information).

2.1 Adjudicated cardiac thrombotic events

The following table includes adjudicated cardiac thrombotic events from the long-term studies (078 and 091, median exposure: 14 months).

Table 3. Patients with adjudicated cardiac thrombotic events in studies 078 and 091*.

	Rofecoxib 25 mg					Placebo				
	Pt years risk	MI		SD	UA	Pt years risk	MI		SD	UA
		fatal	Non- fatal				fatal	Non- fatal		
091	301	1	1	1	0	366	0	4	1	1
078	966	1 ¹	5	4	0	1098	0	7	2	4
Total	1267	8		5	0	1464	11²		3	5

Source: sponsor’s table. SUR and 2/19/02 submission. *Median exposure: 14 months. N = randomized. MI: myocardial infarction. SD: sudden death. UA: unstable angina. Patients with more than one event are listed under the most serious event. ¹This patient also had unstable angina. ²Three of these patients also had unstable angina.

Reviewer’s comment: There was no excess of MI in the rofecoxib 25 mg daily group, as compared to the placebo group.

As noted above, there was an imbalance in the number of CV thrombotic cases referred for adjudication that had “insufficient information” in this database (18 and 4 in the rofecoxib and placebo groups, respectively). If we were to take into consideration those patients for which the investigator, the medical records or the FDA reviewer had entertained the diagnosis of a myocardial infarction but there was insufficient information, the numbers would still suggest

no increased risk of MI in the rofecoxib 25 mg group as compared to placebo in this population.

2.2 Cerebrovascular and peripheral thrombotic events in Alzheimer's studies

Table 5. Patients with adjudicated cerebrovascular and peripheral events in study 078 and 091.

	N	TIA	Ischemic stroke	Arterial thromboses	Venous thromboses
Rofecoxib 25 mg	1267	3	3	0	0
Placebo	1464	2	12	1	2

N: patients randomized. Source: Adjudication packages from 7/12/01 submission and 9/19/02 submission.

Reviewer's comment: The numbers suggest an excess of cerebrovascular thrombotic events in the placebo group as compared to the rofecoxib group. This finding is difficult to interpret. Review of cases by the division of Neuropharm products is still ongoing.

3. Fluid retention, edema and hypertension

In the Alzheimer's studies, rofecoxib 25 mg daily was associated with increased incidence of fluid retention, edema and hypertension as compared to placebo. (See MO review of 11/28/01). These adverse events are known to occur with all NSAIDs and appear to be dose-related.

Table 6. Summary of HTN, edema and CHF-related events in Alzheimer's studies 091 and 126* (crude rates).

	Rofecoxib 25 mg ¹ N= 726 n (%)	Placebo ² N= 722 N (%)
HTN-related	63 (8.7)	19 (2.6)
Edema-related	21 (2.9)	6 (0.8)
CHF-related	16 (2.2)	6 (0.8)

* Source NDA 21-042/s007 safety update report. Median duration for study 091: one year. Median duration for 126: five months. Data from 078 not provided. ¹ Nine patients discontinued rofecoxib therapy due to the above AE's (3 in each category). ² One patient discontinued placebo due to a HTN- related event.

In the original NDA the 6-month OA database had the following incidence of hypertension-related events: rofecoxib 12.5 mg: 6 %; rofecoxib 25 mg: 7 %; rofecoxib 50 mg: 12 %; ibuprofen 800 mg TID: 5 % and diclofenac 750 mg BID: 3 %.

In the RA efficacy database (NDA s012), in the one-year studies, rofecoxib (both, 25 and 50 mg) was associated with two to three fold increase in the incidence of hypertension-related events as compared to naproxen (15% and 5%, respectively).

Reviewer's comment:

Although these are crude rates and none of the studies were designed to address safety questions, there is a suggestion that rofecoxib at doses recommended for chronic use may be

associated with a higher incidence of HTN-related events than other NSAIDs. Prospective, long-term, parallel studies on hypertension related-events with different NSAIDs are not available.

4. Conclusions:

The Alzheimer's studies described in this memo were not specifically designed or powered to address CV outcomes. However, they provide a relatively large placebo-controlled database (rofecoxib N= 1267, placebo N= 1464), with a median exposure of 14 months and a substantial number of MI and cerebrovascular events for analysis.

In this database, there was no excess for *all* cardiovascular thrombotic events (cardiac, cerebrovascular and peripheral together) and particularly, no excess of MI in the rofecoxib 25 mg group, as compared to placebo. However, total cause mortality (29 vs. 15) and cardiovascular thrombotic deaths (8 and 3) trended against rofecoxib.

These data support the hypothesis that the excess of MI found with rofecoxib 50 mg in the VIGOR study - as well as the trends observed in the ADVANTAGE and the RA databases with the 25 mg dose relative to naproxen - may in part be explained by the lack of an anti-platelet effect of rofecoxib relative to naproxen. However, in addition, the biologically plausible pro-thrombotic effect and the known effects on fluid retention, edema and hypertension may play a role in the different cardiovascular safety profile of rofecoxib as compared to naproxen.

Adequately powered and prospectively designed studies are necessary to definitively address cardiovascular safety issues with VIOXX.

