



Global Research & Development

26 May 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

**Re: Submission to Docket 2004N-0559:
Overall Benefit to Risk Considerations for COX-2 Selective Nonsteroidal
Anti-Inflammatory Drugs and Related Agents**

Dear Docket Management:

Herewith attached find documentation for submission to the subject Docket. This submission reflects additional supportive information provided to the Agency subsequent to the Arthritis & Drug Safety and Risk Management Advisory Committee meeting held February 16-18, 2005.

If there are any additional questions or comments regarding this request, please contact me at (212) 733-1608.

Sincerely,

Ron Guido
Director, Regulatory Affairs
Pfizer, Inc

cc: Ms. Jane Dean, RN, MSN
Division of Anesthetics, Analgesic and Rheumatology Products (cover letter)

2004N-0559

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Response to Comments by Curt Furberg, MD, PhD

Drug Safety and Risk Management Advisory Committee

February 16-18, 2005

At the FDA Advisory Committee on February 16 and 17, Dr. Furberg raised several issues regarding the presentation of valdecoxib data in Pfizer's Briefing Document. Pfizer briefly responded to these issues during the Advisory Committee hearing on February 17. Subsequently, FDA requested that Pfizer respond in writing to these issues. Pfizer appreciates this opportunity to clarify the issues raised by Dr. Furberg. Pfizer strives to present clinical data in a manner that is accurate, complete, and useful to the agency, clinicians, and the public. Pfizer presented extensive information in the Briefing Document, including several analyses of the clinical study databases for celecoxib, valdecoxib, and parecoxib. These analyses provide the most comprehensive picture to date of the cardiovascular safety for these three drugs.

In an effort to provide a complete analysis of these drugs, Pfizer included multiple presentations of the available data. For example, for individual studies or collective analyses, the Briefing Document frequently provides data on common adverse events, serious adverse events, clinically relevant adverse events (CRAEs) adjudicated by independent experts, and other presentations of the available data. As will be demonstrated below, the issues raised by Dr. Furberg largely stem from a misunderstanding about the nature or clarity of these data presentations, attempts to compare two disparate sets of data, or reasonable disagreements among scientists about how data should be presented or analyzed.

Comment 1

Studies were excluded from the integrated summaries of safety (ISS) analyses.

In Section 3.3 of the FDA Briefing Document (p.55), the first paragraph states:

Cardiovascular and cardiorenal safety data from 18 clinical studies that were conducted to treat acute pain in a variety of surgical settings and ankle sprain were integrated for evaluation; these integrated data represent 4087 patients treated with valdecoxib 20-60 mg TDD and 2468 patients treated with placebo.

In Section 3.6 of the FDA Briefing Document (p.76), the second bullet point states:

Analysis of integrated safety data from 20 completed clinical studies, representing 4689 patients treated with valdecoxib \geq 20 mg TDD, shows no cardiovascular safety risk associated with valdecoxib treatment when used for up to 14 days in acute post-surgical settings (Section 3.3).

Response to Comment 1

Section 3.3 of the FDA Briefing Document (p.55) refers to 4087 patients treated with valdecoxib **20-60 mg TDD** in 18 clinical studies. In Section 3.6 of the FDA Briefing Document (p.76), the second bullet point for the overall conclusions on valdecoxib cardiovascular safety refers to 4689 patients treated with valdecoxib ≥ 20 mg TDD in 20 clinical studies. Although both of these references are, in fact, accurate, they are derived from two different data summaries recently performed by Pfizer.

The first of these was prepared for a planned valdecoxib acute pain NDA submission, for which a detailed analysis of valdecoxib 20-60 mg dosing was performed. That submission included an Integrated Summary of Safety (ISS) analysis of 20 studies with 4689 patients treated with valdecoxib ≥ 20 mg TDD, but focused in detail on 18 of the studies that used 20-60 mg TDD valdecoxib, which was the proposed dose range for the indication. There was a less in-depth analysis of the entire pooled group of 20 studies, which included some studies with the 80 mg valdecoxib dose.

The second of these was prepared for the European Medicines Agency (EMA) and included the same 20 studies as the planned valdecoxib acute pain submission. However, in addition to the 20–60 mg analysis, the EMA submission also included an additional focused summary of the 80 mg dose, which was of relevance since this was an approved dose of parecoxib. This summary included all of the clinical experience at the 80 mg dose, as well as the relevant placebo groups.

For the FDA Briefing Document, the decision was made to use the more in-depth integrated data analysis for the 20-60 mg TDD target therapeutic dose range (defined in the planned NDA acute pain submission) derived from 18 studies. Data from 2 studies with only 80 mg valdecoxib dosing (Studies 93-035 and 072) were, therefore, not included in that pooled FDA Briefing Document analysis.

However, because one of these 80 mg studies, Study 93-035 in patients with coronary artery bypass surgery (CABG), showed a cardiovascular signal, it was specifically discussed in Section 3.4.2.1 (pp.65-66) of the Briefing Document. This study contained the highest incidences of adverse cardiovascular events, an experience which could arguably have been diluted by inclusion in a pooled 20-80 mg TDD presentation, or even in an analysis of the total clinical experience at 80 mg TDD (as illustrated in the table below), since the other 80 mg studies essentially showed no findings different from placebo (see “Without Study 93-035” column in table). Pfizer understands that the rationale behind the chosen presentation was not obvious to the reader of the Briefing Document, but notes that the purpose of the analysis in Section 3.3 was to examine cardiovascular safety of valdecoxib at the doses that would be proposed for an acute pain indication, while separately discussing the cardiovascular signal that was observed in Study 93-035. Additionally, Pfizer notes that the conclusions regarding cardiovascular safety from the Briefing Document, the EMA analysis and the ISS analysis were similar, despite the differences between numbers of studies included in each.

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Cardiovascular Adverse Events: Surgery Studies with a Valdecoxib 80 mg Total Daily Dose (TDD) Group

Adverse Event Category Adverse Event	All Studies Combined		Without Study 93-035		Study 93-035 Alone	
	Placebo N = 466	80 mg ^a N = 602	Placebo N = 337	80 mg ^a N = 335	Placebo N = 129	80 mg ^a N = 267
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cardiovascular Thromboembolic	2 (0.4)	8 (1.3)	0 (0.0)	2 (0.6)	2 (1.6)	6 (2.2)
Myocardial	2 (0.4)	2 (0.3)	0 (0.0)	1 (0.3)	2 (1.6)	1 (0.4)
Myocardial infarction	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.8)	0 (0.0)
Myocardial ischemia	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)
Tachycardia ventricular	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.4)
Cerebrovascular	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)
Cerebrovascular disorder	0 (0.0)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)
Peripheral vascular	0 (0.0)	4 (0.7)	0 (0.0)	1 (0.3)	0 (0.0)	3 (1.1)
Pulmonary embolism	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Deep thrombophlebitis	0 (0.0)	3 (0.5)	0 (0.0)	1 (0.3)	0 (0.0)	2 (0.7)
Cardiorenal						
Cardiac failure	1 (0.2)	3 (0.5)	0 (0.0)	0 (0.0)	1 (0.8)	3 (1.1)
Hypertension	8 (1.7)	8 (1.3)	8 (2.4)	8 (2.4)	0 (0.0)	0 (0.0)
Hypertension aggravated	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.4)
Edema generalized	1 (0.2)	2 (0.3)	0 (0.0)	0 (0.0)	1 (0.8)	2 (0.7)
Edema peripheral	8 (1.7)	16 (2.7)	1 (0.3)	0 (0.0)	7 (5.4)	16 (6.0)
Face edema	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)
Other Cardiovascular-Related^b	37 (7.9)	51 (8.5)	23 (6.8)	22 (6.6)	14 (10.9)	29 (10.9)
Atrial arrhythmia	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	2 (1.6)	1 (0.4)
Bradycardia	4 (0.9)	2 (0.3)	2 (0.6)	2 (0.6)	2 (1.6)	0 (0.0)
Cardiac failure	1 (0.2)	3 (0.5)	0 (0.0)	0 (0.0)	1 (0.8)	3 (1.1)
Fibrillation atrial	2 (0.4)	6 (1.0)	0 (0.0)	0 (0.0)	2 (1.6)	6 (2.2)
Hematoma NOS	3 (0.6)	4 (0.7)	3 (0.9)	1 (0.3)	0 (0.0)	3 (1.1)
Hypertension	8 (1.7)	8 (1.3)	8 (2.4)	8 (2.4)	0 (0.0)	0 (0.0)
Hypotension	8 (1.7)	13 (2.2)	8 (2.4)	11 (3.3)	0 (0.0)	2 (0.7)
Tachycardia	5 (1.1)	10 (1.7)	3 (0.9)	2 (0.6)	2 (1.6)	8 (3.0)

^a Indicates valdecoxib total daily dose; adverse event totals include for Study 93-035 only events that occurred during follow-on valdecoxib treatment and not events that occurred during the preceding parecoxib sodium treatment period.

^b Only events that occurred in $\geq 1\%$ of treated patients are presented in this table for this category.

Note: Adverse events occurring beyond 7 days after last dose are not included in the analysis.

Source: EMEA Valdecoxib Response (Table 16); EMEA/H/A-18/633.

Comments 2 and 3

There were discrepancies between numbers of events across tables.

The definitions and diagnostic criteria for myocardial infarctions varied across the material presented.

Response to Comments 2 and 3

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Dr. Furberg commented that there are different numbers of myocardial infarction reported for placebo in valdecoxib acute pain studies in Tables 19 (0 patients) and 20 (1 patient) of the FDA Briefing Document.

Table 19 is a summary table of cardiovascular-related adverse events, **regardless of seriousness**, in the combined acute pain studies, of which there were 0 myocardial infarctions for placebo and 3 for valdecoxib. In contrast, Table 20 is a summary of all patients with **serious** adverse events in the combined acute pain studies, of which there were 1 for placebo and 3 for valdecoxib

The difference between the incidences of adverse events in these two tables is due to the following data handling conventions: adverse events with onset more than 7 days after the last dose of study medication were excluded from summary tables (e.g., Table 19), except for the summary tables of serious adverse events (e.g., Table 20), which included all adverse events that occurred during the treatment period, as well as those that occurred within 30 days of the last dose of study medication.

Another difference between Tables 19 and 20 was the classification of cardiac failure. Cardiac failure was not categorized as a cardiorenal adverse event in Table 19, whereas, it was categorized as a cardiorenal adverse event in Table 20 (in addition to also being classified in the “other cardiovascular-related adverse events” category). This difference was inadvertent and was not the result of a logical medical decision and so can be considered an error. It was not an attempt to suppress important safety information, as cardiac failure data were presented in Table 20.

For both Tables 19 and 20, cardiac failure was considered to be in the “other cardiovascular-related adverse events” category. If all of the adverse events within this category had been included in Table 19, it would have contained a large number of events that occurred infrequently. For better presentation of the events within this category, it was decided to use a data cut-off of $\geq 0.2\%$ (or $p < 0.10$). Therefore, cardiac failure did not make this cut-off and is not shown in Table 19. Table 20 lists serious adverse events, which were fewer in number, and so no data cut-off was required. Pfizer recognizes that the distinction between these data sets was not fully described in the Briefing Document, and a more clear description in the Briefing Document of these differences in data collection could have prevented this misunderstanding.

Dr. Furberg also stated the following: “What is more striking is when you start looking at the individual studies that contributed to the summary statistics for the 19 studies, I just looked at two to them. The study we just talked about, the general surgery study, in terms of myocardial infarction and how you define it, there were three, if you include cardiac arrest and sudden cardiac death, it is six to zero. The summary statistics was zero to three or one to three. Here I have six in one study. I add in the data from one of the bypass surgery trials and I get additional numbers. Just by combining the bypass surgery trial 071 and general surgery, for MI I have zero to 8 or 1 to 9, not 1 to 3. How about the other 16 studies? That is troubling.”

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By combining data from tables presented in several sections of the FDA Briefing Document, Dr. Furberg suggests that tables in the Briefing Document contain discrepancies between data for cardiovascular thromboembolic events. Specifically, he notes differences in the numbers of cardiovascular adverse events presented in Tables 19, 20, 25 and 26 in the Briefing Document. These differences can be explained as follows:

- As noted above, Tables 19 and 20 present distinctly different information on cardiovascular adverse events (i.e., as reported by investigators and coded with WHOART conventions): Table 19 summarizes cardiovascular-related adverse events, **regardless of seriousness**, and with a 7-day cutoff, while Table 20 summarizes only **serious** cardiovascular-related adverse events with a 30-day cut-off. As explained above, the data-handling conventions used to derive these two tables are not identical; thus, the information in the tables is not expected or intended to be identical. Also as specified in the text, this grouping of studies included cardiovascular adverse events or serious cardiovascular adverse events from the valdecoxib treatment period from Studies 93-069 and 93-071.
- The two tables to which Dr. Furberg refers, Tables 25 and 26, are presentations of clinically relevant adverse events (CRAEs) for individual Studies 93-071 and 93-069. These tables were part of a series (Tables 24-27) evaluating CRAEs for the IV and PO treatment periods combined and for the IV and PO treatment periods separately for Study 93-071 (Tables 24 and 25) and Study 93-069 (Table 26 and 27). The incidence of patients with CRAEs was a primary safety endpoint in these 2 studies. These analyses were intended to dissect out, as best as possible, the safety effects of oral dosing with valdecoxib and parenteral dosing with parecoxib sodium, and to compare the safety of treatment regimens of parecoxib sodium followed by valdecoxib, placebo followed by valdecoxib, and placebo. Adverse events that occurred in the IV dosing period were therefore assigned to parecoxib sodium treatment, and adverse events that occurred during the PO dosing period were assigned to valdecoxib treatment.

On the other hand, as noted in Section 3.3.1 (p.56) of the Briefing Document, Tables 19 and 20 for the acute pain meta-analysis contained only data from the PO treatment periods (valdecoxib or placebo) of studies that included parecoxib sodium IV treatment followed by valdecoxib PO treatment. Therefore, only cardiovascular-related adverse events that occurred during valdecoxib 20-60 mg and placebo treatment were included in Tables 19 and 20, as noted in the table titles and column headers. Cardiovascular-related adverse events that occurred with parecoxib sodium treatment are presented in the tables described separately for Studies 93-071 (Section 3.4.2.2) and 93-069 (Section 3.4.2.3).

- As described in the Briefing Documents (Section 3.4.1, pp.63-64), CRAEs were prospectively defined before protocol approval and adjudicated by a panel of independent experts in order to evaluate a potential cardiovascular safety signal in Studies 93-069 and 93-071, as well as Study 93-035. Additionally, CRAE definitions were discussed with and approved by the FDA for Studies 069 and

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071. Therefore, CRAEs represent a safety endpoint that is distinct from adverse event reporting by investigators. Cardiovascular thromboembolic CRAEs were defined as follows: cardiac events (myocardial infarction, severe myocardial ischemia, cardiac arrest, or sudden cardiac death); cerebrovascular events (acute ischemic or hemorrhagic stroke, hemorrhagic infarction, or transient ischemic attack); and peripheral vascular events (vascular thrombosis [lower limb deep vein thrombosis], or pulmonary embolism). All adverse events (including serious adverse events) were coded using the WHOART dictionary. Events adjudicated by the CRAE expert panel and categorized into one of the above CRAE definitions may have been derived from a number of signs and symptoms reported as adverse events and coded to WHOART terms for those signs and symptoms. It is expected that adjudicated adverse events will differ from the raw adverse event counts from which they are derived, which is why studies are adjudicated in the first place.

Dr. Furberg also stated the following: "I also find that they included in summary statistics one of the bypass surgery trials but not the other one. Why? I mean, in the other trial, it met the same definition; If you put that in, the numbers get even worse. There is clearly an underreporting of events."

Two coronary artery bypass graft (CABG) surgery trials were conducted with valdecoxib: 93-035 and 93-071. Study 93-071 evaluated valdecoxib 40 mg TDD, a dose within the 20-60 mg TDD defined range for studies included in the integrated analysis conducted for the FDA Briefing Document. Therefore, Study 93-071 was included in the integrated analysis, and is also described separately in Section 3.4.2.2 of the FDA Briefing Document.

In contrast, Study 93-035 evaluated valdecoxib only at a dose of 80 mg TDD, which was beyond the 20-60 mg TDD defined therapeutic dose range for studies included in the integrated analysis for the FDA Briefing Document. Therefore, Study 93-035 was not included in the integrated analysis; however, it was described separately in Section 3.4.2.1 of the FDA Briefing Document, with emphasis on cardiovascular events. Study 93-071 and its cardiovascular events were also described separately, in addition to being included in the pooled analysis because the doses being used were those intended for use had the acute pain NDA been filed and approved.

Comment 4

There were discrepancies in various meta-analyses of chronic pain trials.

Response to Comment 4

Comparison to Ott et al. (2003) Publication

Dr. Furberg suggests that there are discrepancies between data summarized in the FDA Briefing Document for Study 93-035 (Section 3.4.2.1) and data presented in a publication on Study 93-035 by Ott et al. (*J Thorac Cardiovasc Surg.* 2003;125:1481-1492). Specifically, Dr. Furberg makes a comparison between Table 22 in the FDA Briefing

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Document, which is a summary of cardiovascular and cardiorenal CRAEs reported during both IV (parecoxib sodium) and PO (valdecoxib) dosing periods in Study 93-035, and Table 5 from the Ott et al. publication, which is a summary of serious adverse events occurring in 2 or more patients in any treatment group. Because the numbers of myocardial infarctions differ in these 2 tables, Dr. Furberg suggested that Pfizer reduced the number of adverse events by retroactively applying excessively strict diagnostic criteria in the CRAE analysis presented in the FDA Briefing Document.

In fact, a review of the Ott et al. publication, combined with the information provided in the Response above regarding CRAEs, provides a clear explanation of these differences. Table 5 in Ott et al. lists 1 myocardial infarction reported in the standard care treatment group and 5 myocardial infarctions reported in the parecoxib/valdecoxib treatment group, based on the analysis of serious adverse events. However, Ott et al. also explain that 4 of the 5 myocardial infarctions in the parecoxib/valdecoxib treatment group “were given a diagnosis in the immediate perioperative period (within 24 hours of surgical intervention)”. Table 22 of the FDA Briefing Document presents 1 myocardial infarction in the placebo treatment group and 1 myocardial infarction in the parecoxib sodium/valdecoxib treatment group. The clinical study report for Study 93-035 explains that only 2 reported myocardial infarctions (1 in the placebo group and 1 in the parecoxib sodium/valdecoxib group) were adjudicated by an independent panel of experts as meeting the predefined criteria for a CRAE; other reported myocardial infarctions either did not meet the criteria or occurred prior to drug administration (this panel carried out their deliberations as the trial was being conducted, i.e., prior to blind breaking). Therefore, the number of adjudicated cardiovascular CRAEs reported in the study report (and reported in the FDA Briefing Document) does not match the number of non-adjudicated serious adverse events reported by Ott et al.

Comparison to White et al. (2004) Publication

Dr. Furberg suggests that data from Table 14 in the FDA Briefing Document be compared to data from Table 2 in a White et al. (*Am J Ther.* 2004;11:24-250) publication. He notes that Table 14 lists 10 reports of cardiovascular thromboembolic adverse events during valdecoxib treatment and 2 adverse events during placebo treatment, compared to 17 reports and 2 reports, respectively, in the White et al. article. Making the same comparison for myocardial infarction, he notes 5 reports in the valdecoxib treatment group and 1 in the placebo treatment group in the FDA Briefing Document Table 14, compared to 6 reports and 1 report, respectively, in the White et al. publication. He questions this discrepancy, considering that the FDA Briefing Document analysis included 19 studies and the White et al. analysis included only 10 studies.

Table 2 from the White et al. article and Table 14 from the FDA Briefing Document were not derived from the same set of valdecoxib chronic pain studies. For example, Table 14, a partial presentation of the data from the chronic pain studies analysis, included only studies with a placebo treatment arm, while Table 2 from White et al. included studies with and without a placebo treatment arm. A better (but not totally accurate) comparison would have been with Table 15 in the Briefing Document, which provided additional analysis by comparing treatment with valdecoxib ≥ 10 mg TDD to treatment with non-

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selective NSAIDs. All of the White et al. studies were included in the analysis for Table 15, in addition to one other study, and it is apparent that the numbers of cardiovascular thromboembolic events in valdecoxib-treated patients are more similar between these 2 tables: for example, 17/4531 patients in the White et al. table and 17/4591 patients in Table 15. However, direct comparisons between any of these 3 tables are not valid because each of the 3 tables had a distinct data source.

Comment 5

The Alzheimer's trial was excluded from the meta-analysis of celecoxib safety data.

Response to Comment 5

Dr. Furberg claims that the Alzheimer's Disease trial, Study IQ5-97-02-001, was excluded from the placebo-controlled meta-analysis of celecoxib studies in chronic indications, and specifically from the data presented in Table 4 of the FDA Briefing Document. It is unclear to what he is referring here. As indicated in Table 1 of the FDA Briefing Document, Study IQ5-97-02-001 was included in the meta-analysis of data from celecoxib studies in chronic indications, as was the long-term extension of this trial, Study EQ5-98-02-002.