Advisory Committee Briefing Document

Valdecoxib: Cardiovascular Safety, Skin Reactions, and Benefit/Risk Assessment

In Preparation for a Public Forum on Selective COX-2 Inhibitors

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ABBREVIATIONS

ADAPT	Alzheimer's Disease Anti-Inflammatory Prevention Trial
AERS	Adverse Event Reporting System
APC	Prevention of Sporadic Colorectal Adenomas with Celecoxib Trial
APPROVe	Adenomatous Polyp Prevention on Vioxx Trial
APTC	Antiplatelet Trialists' Collaboration
BID	Twice Daily
CHMP	Committee on Medicinal Products for Human Use
CI	Confidence Interval
CLASS	Celecoxib Long-Term Arthritis Safety Study
COX-1	Cyclooxygenase-1
COX-2	Cyclooxygenase-2
CSC	Cardiovascular Safety Committee
DEP	Dermatology Expert Panel
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
EM	Erythema Multiforme
EMEA	European Medicines Agency
EU	European Union
FAP	Familial Adenomatous Polyposis
FDA	Food and Drug Administration
GPRD	General Practice Research Database
ICD	International Classification of Diseases
IRG	Independent Research Grant
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of Patients With Events
N	Number of Patients Treated
NA	Not Applicable
NCI	National Cancer Institute
NDA	New Drug Application
NSAID	Non-Steroidal Anti-Inflammatory Drug
OA	Osteoarthritis

ABBREVIATIONS, continued

PreSAP	Prevention of Colorectal Sporadic Adenomatous Polyps Trial
QD	Once Daily
RA	Rheumatoid Arthritis
SAP	Spontaneous Adenomatous Polyposis
SCAR	Severe Cutaneous Adverse Reaction
SJS	Stevens-Johnson Syndrome
SR	Sustained Release
SUCCESS	Successive Celecoxib Efficacy and Safety Study
TDD	Total Daily Dose
TID	Three Times Daily
TPD	Therapeutic Products Directorate
TXA_2	Thromboxane
TEMC	Treatment Effects Monitoring Committee
TEN	Toxic Epidermal Necrolysis
UK	United Kingdom
US	United States
VIGOR	Vioxx Intestinal Outcomes Research Trial
WHO	World Health Organization
WHOART	World Health Organization Adverse Reaction Terminology
WOMAC	Western Ontario and MacMaster Universities Osteoarthritis Index

1. INTRODUCTION

1.1. Background

Patients seeking relief in chronic painful conditions such as osteoarthritis (OA) and rheumatoid arthritis (RA) or in acute conditions ranging from dysmenorrhea to post-surgical pain can benefit from effective pain relief using any of a variety of non-opiate analgesic and/or anti-inflammatory medications, including acetaminophen, naproxen, diclofenac, ibuprofen, piroxicam, and celecoxib. With any of these medications, benefit/risk considerations may vary according to clinical setting (eg, chronic versus acute pain) and according to patient characteristics such as baseline risk for gastrointestinal or cardiovascular adverse effects. Valdecoxib, a diaryl-substituted pyrazole, is a selective inhibitor of the inducible form of the enzyme cyclooxygenase (COX-2), which catalyzes the formation of prostaglandins that act as proinflammatory mediators. As a result of this selective COX-2 inhibitory activity, valdecoxib and related medications are believed to provide effective analgesic and anti-inflammatory benefits with less risk of gastrointestinal adverse effects than has been associated with inhibition of both COX-1 and COX-2 using nonselective, non-steroidal anti-inflammatory drugs (NSAIDs). As well as providing effective pain relief, both nonselective NSAIDs and selective COX-2 inhibitors provide a degree of relief from inflammation, making their chronic use necessary for many arthritis sufferers, for whom intermittent use or use of purely analgesic agents like acetaminophen is inadequate. Hence, both nonselective NSAIDs and selective COX-2 inhibitors enjoy extremely widespread use both as prescription arthritis medications and, in the case of some nonselective NSAIDs, as over-the-counter pain relievers.

On 30 September 2004, the selective COX-2 inhibitor rofecoxib (VIOXX®, Merck) was voluntarily withdrawn from worldwide markets after the data safety monitoring board (DSMB) overseeing a long-term, placebo-controlled rofecoxib clinical trial in cancer prevention (the Adenomatous Polyp Prevention on VIOXX [APPROVe] trial) recommended that the trial be suspended because interim data at 18 months indicated that patients treated with rofecoxib had a significantly increased risk of serious cardiovascular events, including myocardial infarction and stroke, compared to patients treated with placebo. On 17 December 2004, the DSMB for the long-term Prevention of Sporadic Colorectal Adenomas with Celecoxib (APC) trial recommended that use of study medication in this trial should be suspended because interim data at 33 months indicated that patients treated with celecoxib had a significantly increased incidence of serious cardiovascular events, including myocardial infarction, stroke, and death compared to patients treated with placebo. In response, the DSMB for another long-term celecoxib sporadic adenomatous polyposis (SAP) prevention trial, the Prevention of Colorectal Sporadic Adenomatous Polyps Trial (PreSAP), recommended suspension of that trial also. However, no statistically significant increase in cardiovascular risk was observed comparing celecoxib treatment versus placebo treatment in the PreSAP trial at 32 months. Also suspended on 17 December 2004 in response to the finding of increased cardiovascular risk with celecoxib in the APC trial was treatment with study medication in the long-term Alzheimer's Disease Anti-Inflammatory Prevention Trial (ADAPT). Although no significant increase in cardiovascular risk was observed comparing celecoxib treatment versus placebo treatment in this trial. Rather, interim data at 18 months from the ADAPT trial indicate that overall cardiovascular risk trended

higher in patients treated with naproxen 220 mg BID or celecoxib 200 mg BID compared to placebo, with naproxen showing the greater numerical increase.

As a result of the observations described above, significant concern has arisen regarding the cardiovascular safety of both selective COX-2 inhibitors and nonselective NSAIDs. Though the cardioprotective effect of aspirin is well-established in medical practice, this effect is attributable to a biochemical activity in platelets (irreversible acetylation of COX-1) that is not shared with other nonselective NSAIDs.[1] There is little evidence that other nonselective NSAIDs are cardioprotective, and cardiorenal effects including increased blood pressure in NSAID users are well known.[2-12] Moreover, in some settings the cardioprotective antiplatelet effect of COX-1 inhibition with aspirin can be offset by increased risk of cerebrovascular hemorrhage; the use of aspirin for primary cardiovascular prevention in low risk subjects is not recommended due to this increase in risk, as established in an Antiplatelet Trialists' Collaboration (APTC) overview of randomized trials in antiplatelet therapy, because for these subjects the benefit/risk balance is not favorable.[13] Conversely, in post-stroke patients, antiplatelet therapy has minor impact on risk of myocardial infarction (reduction of 2 events per 1000 patients) but a large benefit in reduction of risk for ischemic stroke (reduction of 25 events per 1000 patients).[14] For these reasons, the APTC has recommended that cardiovascular and cerebrovascular risk should be evaluated using a composite endpoint that comprises a variety of serious clinical outcomes including myocardial infarction, stroke, pulmonary embolism, and intracerebral or extracerebral hemorrhage.[14]

1.2. Regulatory History

In December 2002, valdecoxib (BEXTRA®) was approved in Canada for acute and chronic treatment of the signs and symptoms of OA and RA at a dose of 10 mg QD, with some patients receiving additional benefits from 20 mg QD, and for the treatment of primary dysmenorrhea at a dose of 40 mg QD. When introduced in Canada, the BEXTRA product monograph contained a contraindication for patients with demonstrated allergic-type reactions to sulfonamides. In December 2002, a "Dear Healthcare Professional" Letter was distributed warning prescribing physicians about this contraindication for use in patients demonstrating allergic reactions to sulfonamides. In December 2004, a second "Dear Healthcare Professional" Letter was sent out to prescribing physicians warning them about a new contraindication for the management of pain post-coronary bypass graft (CABG) surgery, as well as warnings concerning use in patients with ischemic heart disease or other significant risk factors predisposing cardiovascular events. This letter also informed physicians of a Boxed Warning for serious skin reactions to be added to the product monograph. In February 2005, the BEXTRA product monograph was revised to reflect a Boxed Warning for serious skin reactions. In April 2005, following discussions with Health Canada, Pfizer agreed to voluntarily suspend the sale and marketing of BEXTRA (valdecoxib) tablets in Canada.

In November 2001, valdecoxib (BEXTRA®) was approved in the US for treatment of the signs and symptoms of OA and RA at a dose of 10 mg QD, and for the treatment of primary dysmenorrhea at a dose of 20 mg BID/as needed (PRN). On 27 March 2003, valdecoxib (trade names BEXTRA & VALDYN®) was approved for marketing in the European Union (EU) via the centralized procedure. Valdecoxib has been approved in more than 60 countries worldwide (trade names BEXTRA, VALDYNE®, and VALDURE®) for indications that include OA, RA, primary dysmenorrhea, and the management of acute pain, including preoperative dosing for the prevention or reduction of postoperative pain and concomitant administration with opioid analgesics to reduce opioid

requirements. Currently, valdecoxib sales and marketing are suspended in many countries including the US, EU, and Canada.

Parecoxib sodium, a water-soluble prodrug converted metabolically to valdecoxib, was approved for marketing in the European Union (trade names DYNASTAT® and RAYZON®) via the centralized procedure on 22 March 2002 with an indication for the short-term treatment of post-operative pain in adult patients, at an initial dose of 40 mg administered intramuscularly (IM) or intravenously (IV), followed every 6 to 12 hours by 20 mg or 40 mg as required, not to exceed 80 mg/day total daily dose (TDD); for elderly patients or patients with hepatic impairment, the TDD should not exceed 40 mg. Parecoxib sodium is approved for marketing in over 50 countries worldwide for treatment of acute pain or post-operative pain. Because of its COX-2 selectivity, valdecoxib does not affect platelet aggregation, making the soluble prodrug parecoxib sodium suitable for use in perioperative settings without the risk of increased bleeding. Discussion of parecoxib sodium in this document is limited to its use in the 2 CABG surgery studies and the general surgery study described in Section 2.3.

In April 2004, the European Medicines Agency (EMEA), in connection with an Article 31 Referral, completed an Article 31/Article 18 of the benefit/risk of the selective COX-2 inhibitor class of medications (celecoxib, etoricoxib, parecoxib sodium, rofecoxib, and valdecoxib). To support this review, Pfizer provided data concerning the benefit/risk profiles of 3 selective COX-2 inhibitor medications (celecoxib, valdecoxib, and parecoxib sodium), with particular emphasis on gastrointestinal and cardiovascular safety and on skin reactions. Following an extensive review of selective COX-2 inhibitor information available at the time (Opinion: November 2003), the scientific committee of the EMEA, the Committee on Medicinal Products for Human Use (CHMP), considered that the overall benefits of selective COX-2 inhibitors outweighed the risk of adverse reactions for the target patient population.

On 18 November 2004, in the context of the 30 September 2004 worldwide withdrawal of rofecoxib, the European Commission requested comprehensive cardiovascular safety information regarding celecoxib, etoricoxib, lumiracoxib, parecoxib sodium, and valdecoxib to support a second Article 31/Article 18 referral, and on 17 February 2005, the CHMP issued an Urgent Safety Restriction (USR), calling for revisions of prescribing information to include a contraindication for selective COX-2 inhibitors in established ischemic heart disease and/or cerebrovascular disease; the requested revisions are currently being finalized. On 7 April 2005, following discussions with EMEA, Pfizer agreed to a voluntary suspension of sale and marketing of valdecoxib in the EU as a further precautionary measure pending finalization of an assessment of selective COX-2 inhibitors. This was due to concerns on serious skin reactions, which prompted the EU Commission to broaden the scope of the ongoing review of selective COX-2 inhibitors to include questions on serious skin reactions.

At a 16-18 February 2005 joint public meeting of the FDA Arthritis and Drug Safety Advisory Committees, extensive data regarding the cardiovascular safety and benefit/risk of selective COX-2 inhibitors including rofecoxib, celecoxib, and valdecoxib were presented and discussed. By majority vote, the joint Committees recommended that US marketing authorization for rofecoxib, celecoxib and valdecoxib should not be withdrawn, and that prescribing information for each should be strengthened with Boxed Warnings regarding cardiovascular risks. On 7 April 2005, Pfizer agreed to work with FDA to add an acceptable Boxed Warning to the

prescribing information for celecoxib; Pfizer also agreed on 7 April 2005 to a voluntary suspension of sale and marketing for valdecoxib in the US as a precautionary measure pending further discussion with the FDA.

1.3. Content and Organization of Briefing Document

This Briefing Document presents a critical evaluation of the cardiovascular safety of valdecoxib, including comparisons to placebo and, more importantly, to nonselective NSAIDs, the primary therapeutic alternative.

- Comparability between valdecoxib cardiovascular safety and that of nonselective NSAIDs will be demonstrated in a meta-analysis of data from clinical trials up to 1 year in duration (most patients were treated with valdecoxib in studies with up to 3 months duration), although small numbers of events resulted in wide confidence intervals for estimates of relative risk. Cardiovascular safety with valdecoxib in the unique, high-risk setting of coronary artery bypass graft (CABG) surgery will also be discussed.

- Safety analysis of serious skin reactions based on data from clinical studies, epidemiological studies, and spontaneous reports, which are consistent with the medical literature, supports the conclusion that the reporting rate of SCAR with valdecoxib, though several-fold higher than that observed with other selective COX-2 inhibitors, is only marginally worse than the rates observed with some nonselective NSAIDs, and is generally lower than rates observed with anti-epileptic agents.

Separate executive summaries precede the various sections of this briefing document that present cardiovascular safety results from meta-analyses (valdecoxib chronic pain) and skin reactions data from clinical studies, epidemiological studies, and spontaneous reports. In addition, a separate summary of overall cardiovascular safety results for valdecoxib (Section 2.6) follows the respective data presentations, and benefit/risk considerations are discussed at the end of the document (Section 5).

2. VALDECOXIB CARDIOVASCULAR SAFETY

Data presented and reviewed in this evaluation of valdecoxib cardiovascular safety include a Pfizer meta-analysis of data from randomized, controlled clinical trials in chronic pain indications of up to 1 year duration (most patients were treated with valdecoxib in studies with up to 3 months duration) compared to both nonselective NSAIDs and placebo (Section 2.2), and the results of 3 individual clinical trials are discussed (Section 2.3): 2 placebo-controlled trials in CABG surgery patients using sequential treatment with parecoxib sodium/valdecoxib, and 1 placebo-controlled trial in general surgery patients of similar design; results from these 3 studies are also generalized to a larger set of post-surgical studies (Section 2.3.4). Post-marketing experience is presented in Section 2.5. For valdecoxib, there are no clinical trials longer than 1 year in duration, nor are there any published epidemiological studies.

2.1. Valdecoxib Clinical Development Program

The valdecoxib clinical development program has comprised clinical studies in patients with chronic pain conditions including OA, RA, chronic low back pain (CLBP), and cancer pain; in patients with acute pain conditions including general surgery, ankle sprain, CABG surgery, and oral surgery; in patients with dysmenorrhea; and in patients with migraine. Patients in OA, RA, CLBP, and cancer pain (ie, chronic pain) studies were treated with valdecoxib for treatment periods from 2 weeks up to 1 year in duration (most patients were treated with valdecoxib in studies with up to 3 months duration). These patients constitute the clinical study population with the greatest valdecoxib exposure; a meta-analysis of data from 19 chronic pain studies is presented in Section 2.2. For the remaining indications, clinical studies were shorter in duration: the acute pain clinical program included both single-dose studies (post oral-surgery) and multiple-dose studies (general surgery, CABG surgery, and ankle sprain) in which patients were treated with valdecoxib or parecoxib sodium/valdecoxib for durations ranging from 1 to 14 days, and other valdecoxib clinical studies (post-oral surgery, migraine, dysmenorrhea) were conducted in healthier populations or using single-dose, intermittent, or very short-term treatment regimens, and do not provide meaningful data regarding cardiovascular risk. To date, there has been no valdecoxib clinical trial longer than 1 year in duration, and no such study is currently ongoing as of 1 June 2005.

In a separate formal ECG study in patients treated with valdecoxib (Study N91-01-02-109), no drug-related or dose-related changes were apparent for any ECG parameter, including QTc and heart rate. A second study (Study N91-00-08-056), which evaluated ECG data for potential prolongation of QT intervals and for potential correlation with plasma concentrations of valdecoxib, also found no apparent effect on ECG parameters.

2.2. Meta-Analysis of Data From Chronic Pain Studies: Summary

To evaluate the cardiovascular safety of valdecoxib, 19 clinical studies, representing a total of 7061 patients with chronic pain conditions treated with valdecoxib, were identified for meta-analysis. Patients in these 19 studies were treated with valdecoxib at doses ranging from 1 to 80 mg TDD for durations ranging from 2 weeks to 1 year (most patients were treated with valdecoxib in studies with up to 3 months duration); all studies had randomized, parallel-group designs with placebo and/or active comparators (naproxen, diclofenac, ibuprofen, or rofecoxib). Results for all 19 studies that met criteria for meta-analysis either have been published in the medical literature or have been published or otherwise addressed as part of the Pharmaceutical Research and Manufacturers of America (PhRMA) Clinical Study Results Database, available at www.clinicalstudyresults.org.

Endpoints selected for meta-analysis were composites of serious cardiovascular thromboembolic adverse events, myocardial thrombolic events, cerebrovascular events, peripheral vascular events, and the individual adverse events myocardial infarction and stroke, as well as an endpoint approximating the APTC composite endpoint of cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke.[14] Data were also integrated across studies for summarization and comparison of cardiorenal adverse events categorized as follows: hypertension/hypertension aggravated; edema/edema generalized/edema peripheral; and cardiac failure/cardiac failure left/cardiac failure right. Endpoints were derived using World Health Organization Adverse Reaction Terminology (WHOART) medical dictionary terms and were not adjudicated.

The results of this meta-analysis of cardiovascular thromboembolic adverse events and cardiorenal adverse events support the following conclusions:

- The risk of serious cardiovascular thromboembolic events and the risk of events comprising the APTC-like composite endpoint in patients treated with valdecoxib are similar to those observed in patients treated with nonselective NSAIDs or placebo. However, due to limited exposure to study medication and small numbers of events, comparisons between valdecoxib and nonselective NSAIDs or placebo are of very limited value for the statistical evaluation of cardiovascular effects.

- As expected, percentages of patients with hypertension and edema were greater among patients treated with valdecoxib compared to patients treated with placebo. Percentages of patients with these events were similar when patients treated with valdecoxib were compared to patients treated with nonselective NSAIDs. Cardiac failure adverse events were similarly rare regardless of treatment.

The results of this meta-analysis of 19 chronic pain studies are consistent with the results observed in a meta-analysis of cardiovascular safety data from 10 arthritis studies studies recently published:[15] no cardiovascular safety signal was observed for valdecoxib, at any dose, in either case.

2.2.1. Chronic Pain Studies Included in Meta-Analysis

A full list of all Pfizer-sponsored valdecoxib clinical studies was compiled using information from the Pfizer Corporate Clinical Trials Registry and from appropriate legacy Pharmacia sources. Data from studies satisfying the following criteria were included in the meta-analysis:

- Randomized, controlled clinical trial with parallel-group study design;
- Planned duration of treatment ≥2 weeks;
- One or more of the following comparators: placebo, nonselective NSAID(s) (ie, naproxen, diclofenac, ibuprofen), or rofecoxib;
- Database, final study report, and supportive documents available as of 31 October 2004.

Open-label studies, pharmacokinetic studies, clinical pharmacology studies, and drug-drug interaction studies were excluded from the meta-analysis, as were studies of valdcoxib in the treatment of acute pain. The full list of 19 valdecoxib studies included in the meta-analysis is presented in Table 1; collectively, these studies provide a comprehensive analysis of cardiovascular safety for patients exposed to valdecoxib for up to one year of treatment; the meta-analysis does not address cardiovascular safety in patients with durations of exposure to valdecoxib >1 year. In these 19 chronic pain studies, valdecoxib doses ranged from 1 to 80 mg TDD, and doses of active comparator medications were consistent with the current standard of care for OA and RA (naproxen 1000 mg TDD, diclofenac 150 mg TDD, ibuprofen 2400 mg TDD, and rofecoxib 25 mg TDD); all patients treated with valdecoxib 80 mg TDD were enrolled in cancer pain studies. The predominant exposure to valdecoxib was in the range of 10 to 40 mg TDD, including and exceeding doses recommended for OA and RA patients (10 to 20 mg TDD); the predominant NSAID exposure was to naproxen. Eleven of the 19 studies included in the meta-analysis were 3 months or longer in duration; none were longer than 1 year in duration.

Results for all 19 studies that met criteria for meta-analysis either have been published in the medical literature or have been published or otherwise addressed as part of the Pharmaceutical Research and Manufacturers of America (PhRMA) Clinical Study Results Database, available at www.clinicalstudyresults.org.

Table 1. Valdecoxib Chronic Pain Studies Included in Meta-Analysis

Indication Protocol ID	Duration of Treatment	Treatment groups (all medications oral)
Osteoarthritis or Rheumatoid Arthritis		
N91-97-02-015	6 weeks	Placebo, Valdecoxib 0.5 mg BID, 1.25 mg BID, 2.5 mg BID, 5 mg BID, 10 mg QD, 10 mg BID, Naproxen 500 mg BID
N91-97-02-016	6 weeks	Placebo, Valdecoxib 0.5 mg BID, 1.25 mg BID, 2.5 mg BID, 5 mg BID, 10 mg QD, 10 mg BID, Naproxen 500 mg BID
N91-99-02-047	26 weeks	Valdecoxib 20 mg QD, 40 mg QD, Naproxen 500 mg BID
N91-98-02-048	12 weeks	Placebo, Valdecoxib 10 mg QD, 20 mg QD, Ibuprofen 800 mg BID, Diclofenac 75 mg BID
N91-99-02-049	12 weeks	Placebo, Valdecoxib 5 mg QD, 10 mg QD, Naproxen 500 mg BID
N91-99-02-053	12 weeks	Placebo, Valdecoxib 5 mg QD, 10 mg QD, 20 mg QD, Naproxen 500 mg BID
N91-99-02-060	12 weeks	Placebo, Valdecoxib 10 mg QD, 20 mg QD, 40 mg QD, Naproxen 500 mg BID
N91-99-02-061	12 weeks	Placebo, Valdecoxib 10 mg QD, 20 mg QD, 40 mg QD, Naproxen 500 mg BID
I91-99-02-062	26 weeks	Valdecoxib 20 mg QD, 40 mg QD, Diclofenac 75 mg BID
I91-99-02-063	12 months	Valdecoxib 10 mg QD, 20 mg QD, Diclofenac 75 mg BID
872-IFL-0513-004	6 weeks	Placebo, Valdecoxib 20 mg QD, Rofecoxib 25 mg QD
VALA-0513-142	2 weeks	Placebo, Valdecoxib 10 mg QD, Rofecoxib 25 mg QD
VALA-0513-143	2 weeks	Placebo, Valdecoxib 10 mg QD, Rofecoxib 25 mg QD
Chronic Low Back Pain		
N91-01-02-097	4 weeks	Placebo, Valdecoxib 40 mg QD
N91-01-02-108	4 weeks	Placebo, Valdecoxib 40 mg QD
N91-01-02-132	12 weeks	Placebo, Valdecoxib 20 mg QD, 40 mg QD
N91-01-12-133	12 weeks	Placebo, Valdecoxib 10 mg QD, 20 mg QD
Cancer Pain		
N91-01-32-040	12 weeks	Opioid + Placebo BID, Opioid + Valdecoxib 40 mg BID
N91-00-02-079	6 weeks	Opioid + Placebo BID, Opioid + Valdecoxib 20 mg BID, Opioid + Diclofenac 75 mg BID

BID = Twice daily; QD = Once daily

2.2.2. Methodology for Meta-Analysis

2.2.2.1. Categorization of Adverse Events

Adverse events identified for analysis were those reported by investigators treating the respective patients in the 19 clinical studies listed in Table 1. Investigator adverse event terms were coded to preferred terms using a Pfizer (Legacy Searle)-modified WHOART dictionary. Adverse events were not independently adjudicated. For analysis, serious adverse events were summarized if they occurred up to 28 days after the last dose of study medication.

The primary endpoint in this meta-analysis is a composite of serious cardiovascular thromboembolic adverse events. However, for this revised meta-analysis, unlike the preliminary Pfizer meta-analysis submitted to EMEA on 7 January 2005 and to the US FDA on 12 January 2005, the composite endpoint was expanded to include fatal myocardial and cerebrovascular events not included in the previous meta-analysis that were identified by subsequent medical review of cases that previously coded as sudden death (this revised meta-analysis has also been submitted to EMEA [02 March 2005] and to the US FDA [13 May 2005]. Additionally, all cases of stroke in the previous meta-analysis were reviewed medically and identified as having hemorrhagic, ischemic, or unknown cause; as a result of this review, some events that coded as stroke in the previous meta-analysis were categorized as transient ischemic attack in this revised meta-analysis. Therefore, the serious cardiovascular thromboembolic adverse events category was defined for this revised meta-analysis as shown in Table 2, as were various subcategories of events and individual adverse events shown in bold font.

Table 2. Definition of Serious Cardiovascular Thromboembolic Adverse Events Selected as Endpoints for Meta-Analysis

Cardiovascular Thromboembolic		
Myocardial Thromboembolic	**Cerebrovascular**	**Peripheral Vascular**
Angina pectoris aggravated	Aneurysm, Fatal[a]	Embolism
Cardiac arrest	**Stroke**	Embolism Pulmonary
Circulatory Failure	**Stroke, Hemorrhagic**	Peripheral Ischemia
Myocardial Infarction	Cerebrovascular Accident	Thrombophlebitis Leg
Myocardial Ischemia	Cerebrovascular Disorder	Deep Thrombophlebitis Leg
Myocardial Rupture (Post-Infarction)	Cerebral Hemorrhage	
Tachycardia Ventricular	**Stroke, Ischemic**	
Thrombosis Coronary	**Stroke, Unknown**	
Sudden Death, Death Not Otherwise Specified, and fatal cases of Arteriosclerosis, Atrial Fibrillation, Cardiac Failure, Congestive Heart Failure, Coronary Artery Disorder, and Ventricular Fibrillation[a]	Subarachnoid Hemorrhage	
	Subdural Hematoma	
	Transient Ischemic Attack	

Event categories and adverse events indicated in **bold font** were selected as endpoints.

[a] These events were included together with fatal cases of the other events listed in this table to comprise a composite category, **Cardiovascular Death**, that was also selected as an endpoint for meta-analysis.

Additionally, medical review and categorization of all deaths and all investigator-reported cerebrovascular events allowed for an analysis of the APTC-like composite endpoint of cardiovascular deaths plus nonfatal myocardial infarction plus nonfatal stroke (ischemic,

hemorrhagic, or unknown). In the strict definition of the APTC composite endpoint, events comprising the endpoint are adjudicated by independent, blinded experts;[14] no such adjudication was performed for this meta-analysis (reviewers were three Pfizer physicians who were not blinded to randomized treatment assignments for individual patients; none were cardiologists; all were familiar with valdecoxib and NSAID safety).

Cardiorenal adverse events were defined as follows (WHOART terms): hypertension/ hypertension aggravated; edema/edema generalized/edema peripheral; and cardiac failure/cardiac failure left/cardiac failure right.

2.2.2.2. Statistical Methods

Separate analyses of serious cardiovascular adverse events and of cardiorenal adverse events were performed using data from studies comparing valdecoxib versus placebo and from studies comparing valdecoxib versus combined nonselective NSAIDs (naproxen, diclofenac, or ibuprofen, any dose). For each of these comparators, analyses included only data from studies in which that comparator was used; ie, analyses comparing valdecoxib versus placebo were based on data only from studies that included a placebo treatment group, and analyses comparing valdecoxib versus combined nonselective NSAIDs were based on data only from studies that included at least one nonselective NSAID treatment group. Adverse events and serious adverse events with onset >28 days after the last dose of study medication were not included in the meta-analysis, with one exception: in the analysis of time-to-death due to any cause, all deaths were included regardless of time of onset relative to last dose of study medication.

For evaluation of cardiovascular risk associated with valdecoxib treatment, the most important analyses are those comparing patients treated with valdecoxib >10 mg TDD versus patients treated with placebo or nonselective NSAIDs, since these comparisons involve valdecoxib exposure at or above the valdecoxib doses indicated for OA or RA. Statistical methods for summarization and analysis were employed as described below; all tests of significance and confidence intervals for statistical comparisons, where provided, were 2-sided with $\alpha = 0.05$, and no adjustments to Type I error were made for multiple comparisons.

- For serious cardiovascular thromboembolic adverse events, the Cochran-Mantel-Haenszel test, stratified by study, was used to analyze differences in incidence rates (numbers of events per patient-year of treatment) between treatment groups. The relative risk of each respective event (categorized as described in Table 2) was expressed as the ratio of valdecoxib to comparator; also presented are 95% confidence intervals and p-values for statistical tests of the hypothesis that relative risk = 1.0.

- Differences in percentages of patients with cardiorenal adverse events, comparing treatment with valdecoxib versus treatment with either placebo or combined nonselective NSAIDs, were analyzed using Fisher's Exact Test.

2.2.3. Results: Meta-Analysis of Data From Chronic Pain Studies

2.2.3.1. Baseline Patient Characteristics and Exposure to Study Medication

Baseline characteristics for patients in chronic pain studies were generally balanced across integrated treatment groups (Table 3). Mean patient age for patients treated with placebo, valdecoxib (any dose), or NSAIDs (all NSAIDs combined, any dose) ranged from 57 to 59 years across treatment groups, and women in each treatment group outnumber men by approximately 2:1. Use of aspirin was also balanced across treatment groups (13 to 14% of patients). Baseline characteristics were also balanced across valdecoxib dose groups. However, none of these studies were designed to evaluate cardiovascular risk, and randomization was not stratified for cardiovascular risk factors; as a result, there were often imbalances in baseline risk factors or aspirin use in individual studies.

Table 3. Baseline Patient Characteristics, Chronic Pain Studies

Category Characteristic	Treatment Group Placebo N = 2235	Valdecoxib (any dose) N = 7061	Combined NSAIDs (any dose) N = 2323
Age (years)			
Mean	56.6	57.5	58.6
≥ 65 years	678 (30.3)	2191 (31.0)	792 (34.1)
≥ 75 years	161 (7.2)	572 (8.1)	203 (8.7)
Gender, n (%)			
Male	772 (34.5)	2179 (30.9)	657 (28.3)
Female	1463 (65.5)	4882 (69.1)	1666 (71.7)
Indication			
OA/RA	1464 (65.5)	5986 (84.8)	2261 (97.3)
Chronic Low Back Pain	593 (26.5)	897 (12.7)	0 (0.0)
Cancer Pain	178 (8.0)	178 (2.5)	62 (2.7)
Aspirin Use, n (%)	286 (12.8)	949 (13.4)	320 (13.8)

NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, and ibuprofen (combined totals); OA = osteoarthritis; RA = rheumatoid arthritis.

Altogether, the meta-analysis of data from completed clinical trials comparing valdecoxib versus placebo in chronic pain conditions represents a total of 5256 patients treated with valdecoxib compared to 2235 patients treated with placebo, and the meta-analysis of data from completed clinical trials comparing valdecoxib versus NSAIDs in chronic pain conditions represents a total of 5409 patients treated with valdecoxib compared to 2323 patients treated with nonselective NSAIDs (all NSAIDs combined, any dose). The actual duration of study drug exposure for subjects included in these meta-analyses is summarized in Table 4.

Table 4. Duration of Exposure, Meta-Analysis of Studies Comparing Valdecoxib Versus Placebo or NSAIDs

(Number [%] of Patients)

Comparison Duration of Treatment	Valdecoxib (any dose)	Comparator (any dose)
Valdecoxib vs Placebo, N	**5256**	**2235**
≥4 Weeks	3945 (75.1)	1419 (63.5)
≥12 Weeks	1662 (31.6)	592 (26.5)
≥24 Weeks	0 (0.0)	0 (0.0)
Valdecoxib vs Combined NSAIDs, N[a]	**5409**	**2323**
≥4 Weeks	4581 (84.7)	2004 (86.3)
≥12 Weeks	2714 (50.2)	1269 (54.6)
≥24 Weeks	1176 (21.7)	537 (23.1)
≥36 Weeks	355 (6.6)	165 (7.1)
≥52 Weeks	211 (3.9)	99 (4.3)
≥60 Weeks	0 (0.0)	0 (0.0)
Valdecoxib vs Naproxen, N[a]	**3923**	**1343**
≥4 Weeks	3215 (82.0)	1124 (83.7)
≥12 Weeks	1656 (42.2)	684 (50.9)
≥24 Weeks	410 (10.5)	180 (13.4)
≥36 Weeks	0 (0.0)	0 (0.0)
Valdecoxib vs Diclofenac, N[a]	**1486**	**773**
≥4 Weeks	1366 (91.9)	701 (90.7)
≥12 Weeks	1058 (71.2)	486 (62.9)
≥24 Weeks	766 (51.6)	357 (46.2)
≥36 Weeks	355 (23.9)	165 (21.4)
≥52 Weeks	211 (14.2)	99 (12.8)
≥60 Weeks	0 (0.0)	0 (0.0)
Valdecoxib vs Ibuprofen, N[a]	**423**	**207**
≥4 Weeks	369 (87.2)	179 (86.5)
≥12 Weeks	188 (44.4)	99 (47.8)
≥24 Weeks	0 (0.0)	0 (0.0)

N = Number of patients treated with study medication; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, and ibuprofen.

[a] Because some studies included multiple NSAID treatment groups, summing the Ns for valdecoxib-treated patients from comparisons versus individual NSAIDs results in a total that exceeds the N for patients actually treated with valdecoxib (any dose) in NSAID-controlled studies.

2.2.3.2. Serious Cardiovascular Thromboembolic Adverse Events: Valdecoxib Versus Combined Nonselective NSAIDs

The relative risk for serious cardiovascular thromboembolic adverse events, comparing the valdecoxib ≥10 mg TDD treatment group and the combined nonselective NSAIDs treatment group, was not statistically significant for the all patients cohort, for non-users of aspirin, or for aspirin users (Table 5). However, because of small numbers of events and limited exposure to treatment in NSAID-controlled studies, comparisons between treatment with valdecoxib and treatment with nonselective NSAIDs for cardiovascular risk, as well as comparisons stratified for non-users of aspirin versus aspirin users, should be interpreted with caution.

When normalized for patient exposure to study medication in NSAIDs-controlled studies, more serious cardiovascular thromboembolic adverse events occurred among aspirin users (4.9 events per 100 patient-years in the valdecoxib ≥10 mg TDD treatment group and 6.3 events per 100 patient-years in the combined nonselective NSAIDs treatment group) compared to non-users of aspirin (0.8 events per 100 patient-years in the valdecoxib ≥10 mg TDD treatment group and 1.6 events per 100 patient-years in the combined nonselective NSAIDs treatment group). This difference likely reflects differences in baseline cardiovascular risk for aspirin users versus non-users of aspirin.

Table 5. Meta-Analysis of Studies Comparing Valdecoxib ≥10 mg TDD Versus Nonselective NSAIDs: Any Serious Cardiovascular Thromboembolic Adverse Event

Population Treatment Group	N	Exposure (pt-years)	n	Relative Risk (95% CI)	p-Value[a]
All Patients					
Valdecoxib ≥10 mg TDD	4591	1346	18	0.57 (0.28, 1.13)	0.106
NSAIDs	2323	662	15	--	--
Non-Users of Aspirin					
Valdecoxib ≥10 mg TDD	3981	1164	9	0.52 (0.21, 1.27)	0.150
NSAIDs	2003	567	9	--	--
Aspirin Users					
Valdecoxib ≥10 mg TDD	610	182	9	0.61 (0.20, 1.82)	0.374
NSAIDs	320	95	6	--	--

N = Number of patients treated with study medication; n = number of patients with events; CI = Confidence interval; TDD = Total daily dose; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, and ibuprofen (combined totals).
[a] Relative risks and p-values for treatment effect are based on Cochran-Mantel-Haenszel test stratified by study.

In studies comparing valdecoxib ≥10 mg TDD versus nonselective NSAIDs, small numbers of events and limited exposure to study medication resulted in extremely wide confidence intervals for all event subcategories and individual adverse events; therefore, these comparisons should be interpreted with caution (Table 6). However, the relative risk comparing valdecoxib ≥10 mg TDD versus combined nonselective NSAIDs for myocardial infarction was 0.33, indicating a statistically significant difference favoring valdecoxib (p = 0.047) despite a wide confidence interval (95% CI: 0.11 to 0.98).

Table 6. Meta-Analysis of Studies Comparing Valdecoxib ≥10 mg TDD Versus Nonselective NSAIDs: Serious Cardiovascular Thromboembolic Adverse Events

Event Category or Adverse Event	Valdecoxib N = 4591	NSAIDs N = 2323	Relative Risk (95%CI)	p-Value[a]
Any Serious Cardiovascular Thromboembolic	**18**	**15**	**0.57 (0.28, 1.13)**	**0.106**
Any Cardiovascular Death	**3**	**3**	**0.53 (0.13, 2.24)**	**0.391**
Any Myocardial Thromboembolic	**8**	**10**	**0.37 (0.15, 0.91)**	**0.030**
Myocardial Infarction	6	7	0.33 (0.11, 0.98)	0.047
Non-Fatal Myocardial Infarction	5	5	0.39 (0.11, 1.37)	0.143
Fatal Myocardial Infarction	1	2	0.19 (0.02, 1.74)	0.142
Any Cerebrovascular	**8**	**5**	**0.72 (0.24, 2.18)**	**0.557**
Stroke	3	3	0.43 (0.09, 2.05)	0.293
Stroke, Non-Fatal	3	3	0.43 (0.09, 2.05)	0.293
Stroke, Fatal	0	0	NA	NA
Stroke, Hemorrhagic	0	0	NA	NA
Stroke, Ischemic	3	1	1.34 (0.13, 13.37)	0.801
Stroke, Unknown	0	2	NA	0.028
Any Peripheral Vascular	**2**	**1**	**1.37 (0.07, 26.31)**	**0.837**
APTC-like Composite Endpoint	**11**	**10**	**0.49 (0.21, 1.13)**	**0.095**
Death Any Cause	**11**	**9**	**0.81 (0.33, 2.00)**	**0.650**

TDD = Total Daily Dose; N = Number of patients treated with study medication; CI = Confidence interval; APTC-like = Antiplatelet Trialists' Collaboration composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke), not adjudicated; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, and ibuprofen (combined totals).

[a] Relative risks and p-values for treatment effect are based on Cochran-Mantel-Haenszel test stratified by study; p-values ≤0.05 are highlighted in gray.

2.2.3.3. Serious Cardiovascular Thromboembolic Adverse Events: Valdecoxib Versus Placebo

The relative risk for serious cardiovascular thromboembolic adverse events, comparing the valdecoxib ≥10 mg TDD treatment group and the placebo treatment group, was not statistically significant for the all patients cohort, for non-users of aspirin, or for aspirin users (Table 7). However, because of small numbers of events and limited exposure to treatment in placebo-controlled studies, comparisons between valdecoxib treatment and placebo treatment for cardiovascular risk, as well as comparisons stratified for non-users of aspirin versus aspirin users, should be interpreted with caution.

When normalized for patient exposure to study medication in placebo-controlled studies, more serious cardiovascular thromboembolic adverse events occurred among aspirin users (7.3 events per 100 patient-years in the valdecoxib ≥10 mg TDD treatment group and 5.9 events per 100 patient-years in the placebo treatment group) compared to non-users of aspirin (1.0 events per 100 patient-years in the valdecoxib ≥10 mg TDD treatment group and 0.4 events per

100 patient-years in the placebo treatment group). This difference likely reflects differences in baseline cardiovascular risk for aspirin users versus non-users of aspirin.

Table 7. Meta-Analysis of Studies Comparing Valdecoxib ≥10 mg TDD Versus Placebo: Any Serious Cardiovascular Thromboembolic Adverse Event

Population Treatment Group	N	Exposure (pt-years)	n	Relative Risk (95% CI)	p-Value[a]
All Patients					
Valdecoxib ≥10 mg TDD	4438	655	12	1.75 (0.53, 5.79)	0.359
Placebo	2235	280	3	--	--
Non-Users of Aspirin					
Valdecoxib ≥10 mg TDD	3849	573	6	4.98 (0.65, 38.26)	0.123
Placebo	1949	247	1	--	--
Aspirin Users					
Valdecoxib ≥10 mg TDD	589	83	6	0.54 (0.11, 2.75)	0.457
Placebo	286	34	2	--	--

N = Number of patients treated with study medication; n = number of patients with events; CI = Confidence interval; TDD = Total daily dose.
[a] Relative risks and p-values for treatment effect are based on Cochran-Mantel-Haenszel test stratified by study.

In studies comparing valdecoxib ≥10 mg TDD versus placebo, small numbers of events and limited exposure to study medication resulted in extremely wide confidence intervals for all event subcategories and individual adverse events; therefore, these comparisons should be interpreted with caution (Table 8). The relative risk comparing valdecoxib ≥10 mg TDD versus placebo for deaths due to any cause was 1.82, indicating a statistically significant difference (p = 0.035) despite a wide confidence interval (95% CI: 1.04 to 3.18).

Table 8. Meta-Analysis of Studies Comparing Valdecoxib ≥10 mg TDD Versus Placebo: Serious Cardiovascular Thromboembolic Adverse Events

Event Category or Adverse Event	Valdecoxib N = 4438	Placebo N = 2235	Relative Risk (95%CI)	p-Value[a]
Any Serious Cardiovascular Thromboembolic	**12**	**3**	**1.75 (0.53, 5.79)**	**0.359**
Any Cardiovascular Death	**4**	**1**	**3.07 (0.33, 28.62)**	**0.324**
Any Myocardial Thromboembolic	**6**	**2**	**1.22 (0.23, 6.48)**	**0.818**
Myocardial Infarction	5	1	1.38 (0.17, 11.30)	0.765
Non-Fatal Myocardial Infarction	4	1	1.09 (0.13, 9.43)	0.940
Fatal Myocardial Infarction	1	0	NA	0.582
Any Cerebrovascular	**5**	**1**	**1.97 (0.30, 12.90)**	**0.477**
Stroke	2	1	0.92 (0.13, 6.58)	0.932
Stroke, Non-Fatal	1	1	0.26 (0.02, 3.47)	0.306
Stroke, Fatal	1	0	NA	0.297
Stroke, Hemorrhagic	0	0	NA	NA
Stroke, Ischemic	2	1	0.92 (0.13, 6.58)	0.932
Stroke, Unknown	0	0	NA	NA
Any Peripheral Vascular	**1**	**0**	**NA**	**0.297**
APTC-like Composite Endpoint	**9**	**3**	**1.26 (0.35, 4.46)**	**0.723**
Death Any Cause	**35**	**19**	**1.82 (1.04, 3.18)**	**0.035**

TDD = Total Daily Dose; N = Number of patients treated with study medication; CI = Confidence interval; APTC-like = Antiplatelet Trialists' Collaboration composite endpoint (cardiovascular death plus nonfatal myocardial infarction plus nonfatal stroke), not adjudicated.

[a] Relative risks and p-values for treatment effect are based on Cochran-Mantel-Haenszel test stratified by study; p-values ≤0.05 are highlighted in gray.

2.2.3.4. Cardiorenal Adverse Events

Percentages of patients with cardiorenal adverse events in the hypertension/hypertension aggravated subcategory and the edema/edema generalized/edema peripheral subcategory were significantly greater in the integrated valdecoxib (any dose) treatment group compared to the integrated placebo group. This is to be expected, since NSAIDs, including selective COX-2 inhibitors, are known to have cardiorenal effects.[2-12] Differences in percentages of patients with cardiorenal adverse events in all subcategories were not statistically significant when the integrated valdecoxib (any dose) treatment group was compared to the combined nonselective NSAIDs treatment group.

Table 9. Cardiorenal Adverse Events: Chronic Pain Studies

(Number [%] of Patients)

Comparison Adverse Event Subcategory	Valdecoxib	Comparator	p-Value[a]
Valdecoxib (any dose) Versus Placebo, N[b]	**5256**	**2235**	
Hypertension/Hypertension Aggravated	98 (1.9)	18 (0.8)	<0.001
Edema/Edema Generalized/Edema Peripheral	156 (3.0)	46 (2.1)	0.029
Cardiac Failure/Cardiac Failure Left/Cardiac Failure Right	6 (0.1)	2 (<0.1)	--
Valdecoxib (any dose) Versus NSAIDs, N[c]	**5409**	**2323**	
Hypertension/Hypertension Aggravated	189 (3.5)	74 (3.2)	--
Edema/Edema Generalized/Edema Peripheral	177 (3.3)	82 (3.5)	--
Cardiac Failure/Cardiac Failure Left/Cardiac Failure Right	8 (0.1)	6 (0.3)	--

N = Number of patients treated with study medication; NSAIDs = Nonselective non-steroidal anti-inflammatory drugs, namely naproxen, diclofenac, and ibuprofen (combined totals).

[a] P-values based on Fisher's exact test; p-values ≤0.05 are highlighted in gray; -- indicates p-value >0.20 or cannot be calculated.

[b] Includes only data from studies with placebo comparators.

[c] Includes only data from studies with NSAID comparators.

2.3. Cardiovascular Thromboembolic Adverse Events in CABG Surgery Studies 93-035 and 93-071 and General Surgery Study 93-069: Summary

Studies 93-035 and 93-071 indicate that CABG surgery patients treated with parecoxib sodium/valdecoxib are at higher risk for cardiovascular thromboembolic adverse events (and for deep surgical infections and sternal wound complications) compared to patients treated with placebo/placebo upon a background of standard of care. Therefore, treatment of acute post-surgical pain with parecoxib sodium/valdecoxib is contraindicated following CABG surgery.

- Currently there are no published data regarding the effect of nonselective NSAIDs or selective COX-2 inhibitors other than parecoxib sodium/valdecoxib on cardiovascular risk in post-CABG surgery patients, and hence no way to put the above information into clinical context.

- No cardiovascular safety signal was observed in general surgery patients in Study 93-069 with a parecoxib sodium/valdecoxib treatment regimen similar to that used in CABG Surgery Study 93-071, compared to a placebo/placebo treatment regimen, suggesting that cardiovascular adverse effects are limited to high-risk patients undergoing coronary bypass procedures. A post-hoc analysis looking at analogous serious adverse events across the entire general surgery trial database similarly failed to find an increase in these events with valdecoxib.

2.3.1. Background: Parecoxib Sodium/Valdecoxib Sequential Treatment

To evaluate the extended safety of parecoxib sodium and valdecoxib treatment for acute pain, Pfizer sponsored 3 large clinical studies (Studies 93-035, 93-069, and 93-071) in which patients were treated immediately post-surgery for 3 days with intravenous (IV) parecoxib sodium or placebo, followed by oral valdecoxib or placebo for up to 14 days. Two of these studies (Studies 93-035 and 93-071) were in patients who had undergone CABG surgery, and the remaining study (Study 93-069) was in a general surgery population.

Safety in these 3 studies was evaluated primarily according to a set of clinically relevant adverse events (CRAEs) that were prespecified and adjudicated by a panel of independent experts who were blinded to randomized treatment assignments. For analysis, CRAEs in all 3 studies that occurred up to 30 days after the last dose of study medication were summarized. Cardiovascular CRAEs prespecified for Study 93-035 were: myocardial infarction or severe myocardial ischemia (myocardial events); cerebrovascular accident, transient ischemic attack, or hemorrhage (cerebrovascular events); peripheral arterial occlusion, deep vein thrombosis, or pulmonary embolism (peripheral vascular events); and congestive heart failure or renal failure (cardiorenal events). Subsequent to the observation of a potential cardiovascular safety signal in Study 93-035, Studies 93-069 and 93-071 were initiated to determine whether the observed cardiovascular risk was specific to CABG surgery patients. For Studies 93-069 (general surgery patients) and 93-071 (CABG surgery patients), 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). In addition, renal CRAEs were prespecified as renal failure or severe renal dysfunction.

2.3.2. Coronary Artery Bypass Graft (CABG) Surgery Studies

Patients who have undergone CABG surgery are normally considered to be at high risk for postoperative adverse events due to risks inherent in anesthesia, cardiac surgery, cardiopulmonary bypass pump procedures, and underlying cardiovascular disease. In particular, cardiopulmonary bypass pump procedures, used in the large majority of patients in Study 93-035 and all patients in Study 93-071, are often associated with a systemic inflammatory response syndrome that can be induced by at least 3 mechanisms:[16] exposure of blood to the plastic tubing and oxygenation systems used to maintain extracorporeal circulation; ischemic reperfusion injury to brain, heart, lungs, kidney, and liver caused by periods of aortic cross-clamping; and splanchnic ischemia that may result in the systemic release of endotoxin. In this setting, COX-2 is up-regulated, and TxA_2 appears to be elevated by multiple mechanisms including heparin-protamine interaction;[17] this increase in TxA_2 may be severe enough to cause pulmonary hypertension. Also, cardiopulmonary bypass procedures activate and partially deplete circulating platelets, and platelet regeneration following surgery is markedly increased, resulting in an apparent "aspirin resistance" if aspirin is administered QD only (ie, because the plasma half-life of aspirin is very short, QD administration is insufficient to produce circadian platelet inhibition when new platelets are generated at a rate higher than normal). Interactions between the various pro- and anti-thrombotic and -inflammatory mediators that contribute to these effects and their clinical consequences are not well understood.[16]

In summary, the first few days after cardiopulmonary bypass procedures represent a unique and highly dynamic pro-thrombotic and inflammatory syndrome, with effects on cardiovascular morbidity that are orders of magnitude greater than those seen in other types of surgery,[18] giving rise to complication rates of 15% or higher that affect the heart, brain, kidneys, or intestinal function.[19] Nearly 13% of CABG surgery patients discharged following the procedure are readmitted to the hospital within 30 days due to complications of the surgery, including infection, congestive heart failure, myocardial infarction/ischemia, and arrhythmias.[20]

Demographic characteristics of patients in Studies 93-035 and 93-071 were similar across treatment groups in each study, as well as between studies. The mean patient age by treatment group was approximately 61 years in both studies, more than 90% of the patients in each study were white, and most patients (between 85% and 90% per treatment group) were male. Concomitant aspirin use was required in both studies. Patients in both studies had primary isolated CABG surgery (ie, without associated valvular replacement, aortic reconstruction, or ventriculoplasty) via median sternotomy; for a majority of patients in Study 93-035 (90% in the parecoxib sodium/valdecoxib treatment group and 86% in the placebo/placebo treatment group), and for all of the patients in Study 93-071, CABG surgery procedures included use of a cardiopulmonary bypass pump.

2.3.2.1. Coronary Artery Bypass Graft Surgery Study 93-035

In Study 93-035, treatment with parecoxib sodium/valdecoxib was evaluated at a dose of 80 mg TDD using a double-blind, parallel-group study design with IV treatment (parecoxib sodium or placebo) for at least 3 days followed by oral treatment (valdecoxib or placebo) for a total treatment duration (IV plus oral) of 14 days. Patients with inadequate pain relief at any time during the study were allowed to receive supplemental opioid analgesia consistent with standard of care, and all patients were required to use concomitant low-dose aspirin. Of the 462 patients randomized in Study 93-035, 311 patients were treated with parecoxib sodium/valdecoxib and 151 were treated with placebo/placebo. Approximately 90% of the patients in each treatment group completed study Day 3 (287/311 patients, 92%, in the parecoxib sodium/valdecoxib treatment group and 135/151 patients, 89%, in the placebo treatment group), which was the day of the protocol-scheduled switch from IV to oral medication for those patients who were able to tolerate oral medication.

When cardiovascular CRAEs (major and minor CRAEs summarized together) were evaluated in Study 93-035 for the entire period of treatment (ie, the IV administration period and the oral administration period considered together), results indicated a potential cardiovascular safety signal associated with parecoxib sodium/valdecoxib treatment in CABG surgery patients compared to placebo/placebo treatment (Table 10).

Table 10. Cardiovascular and Renal CRAEs[a] in Coronary Artery Bypass Graft Surgery Study 93-035: IV Parecoxib Sodium and Oral Valdecoxib Dosing Periods Together

(Number [%] of Patients)

Adverse Event or Event Category	Placebo/ Placebo N = 151	Parecoxib Sodium/Valdecoxib N = 311	p-value
Myocardial infarction or severe ischemia	1 (0.7)	1 (0.3)	-
Cerebrovascular accident	1 (0.7)	9 (2.9)	0.177
Deep vein thrombosis	0 (0.0)	3 (1.0)	-
Pulmonary embolism	0 (0.0)	2 (0.6)	-
Congestive heart failure	1 (0.7)	4 (1.3)	-
Renal failure/dysfunction	7 (4.6)	29 (9.3)	0.096

Note: If a patient had more than one event within a category, that patient is counted only once in the overall adverse events total for that category.

- Indicates p >0.20; p-values were calculated using Fisher's exact test.

[a] Includes major and minor clinically relevant adverse events (CRAEs) summarized together. Major CRAEs were defined as death, all cardiovascular events; all gastrointestinal events; infections that required re-operation or parenteral antibiotics, plus all cases of sepsis; renal events associated with serum creatinine >2.0 mg/dL and increased >0.7 mg/dL from baseline. All CRAEs were adjudicated by a panel of independent experts who were blinded to randomized treatment assignments.

When major CRAEs were evaluated separately for the IV dosing period in Study 93-035, a potential cardiovascular safety signal was observed with parecoxib sodium/valdecoxib treatment in CABG surgery patients compared to placebo/placebo treatment, but differences between treatment groups were not statistically significant (Table 11). When evaluated for the entire study (IV and oral dosing periods together), the composite major CRAE endpoint (defined in footnote to Table 11) was significantly more likely in the parecoxib sodium/valdecoxib treatment group compared to the placebo/placebo treatment group; no significant differences were

observed for any major CRAE subcategories or individual adverse events that comprise the composite endpoint.

Table 11. Major CRAEs[a] in the IV Parecoxib Sodium Dosing Period: Coronary Artery Bypass Graft Surgery Study 93-035

(Number [%] of Patients)

Adverse Event or Event Category	Placebo/ Placebo N = 151	Parecoxib Sodium/Valdecoxib N = 311	p-value
Major Clinically Relevant Adverse Event[a]			-
IV Parecoxib Sodium dosing period only	4 (2.6)	17 (5.5)	-
IV and Oral dosing periods together	7 (4.6)	35 (11.3)	0.024
Death			-
IV Parecoxib Sodium dosing period only	0 (0.0)	2 (0.6)	-
IV and Oral dosing periods together	0 (0.0)	4 (1.3)	-
Myocardial infarction or severe ischemia			-
IV Parecoxib Sodium dosing period only	0 (0.0)	1 (0.3)	-
IV and Oral dosing periods together	1 (0.7)	1 (0.3)	-
Cerebrovascular accident			-
IV Parecoxib Sodium dosing period only	0 (0.0)	5 (1.6)	0.178
IV and Oral dosing periods together	1 (1.7)	9 (2.9)	0.177
Deep vein thrombosis			-
IV Parecoxib Sodium dosing period only	0 (0.0)	0 (0.0)	-
IV and Oral dosing periods together	0 (0.0)	3 (1.0)	-
Pulmonary embolism			-
IV dosing period only	0 (0.0)	1 (0.3)	-
IV and Oral dosing periods together	0 (0.0)	2 (0.6)	-
Renal failure/dysfunction			-
IV Parecoxib Sodium dosing period only	3 (2.0)	8 (2.6)	-
IV and Oral dosing periods together	4 (2.6)	8 (2.6)	-
Gastrointestinal event			-
IV Parecoxib Sodium dosing period only	0 (0.0)	0 (0.0)	-
IV and Oral dosing periods together	0 (0.0)	4 (1.3)	-
Infection			-
IV Parecoxib Sodium dosing period only	1 (0.7)	3 (1.0)	-
IV and Oral dosing periods together	1 (0.7)	12 (3.9)	0.069

Note: If a patient had more than one event within a category, that patient is counted only once in the overall adverse events total for that category.
IV = Intravenous.
[a] Major clinically relevant adverse events (CRAEs) were defined as death, all cardiovascular events; all gastrointestinal events; infections that required re-operation or parenteral antibiotics, plus all cases of sepsis; renal events associated with serum creatinine >2.0 mg/dL and increased >0.7 mg/dL from baseline. All CRAEs were adjudicated by a panel of independent experts who were blinded to randomized treatment assignments.
- Indicates p >0.20 or could not be calculated; p-values were calculated using Fisher's exact test.

2.3.2.2. Coronary Artery Bypass Graft Surgery Study 93-071

In Study 93-071, treatment with parecoxib sodium/valdecoxib was evaluated at a dose of 40 mg TDD using a double-blind, parallel-group study design with IV treatment (parecoxib sodium or placebo) for 3 days followed by oral treatment (valdecoxib or placebo) for 7 days; patients with inadequate pain relief at any time during the study were allowed to receive supplemental opioid analgesia consistent with standard of care, and all patients were required to use concomitant low-dose aspirin. To ensure equal distribution across treatment groups, patients were stratified by baseline cardiovascular risk (eg, aspirin use, history of cerebrovascular accident, and other risk factors such as history of myocardial infarction) into either a high or low risk group. Of the 1671 patients randomized in Study 93-071, 544 patients received parecoxib sodium/valdecoxib, 544 patients received placebo/valdecoxib, and 548 patients received placebo/placebo treatment. The remainder of the patients were randomized but did not receive study medication. Between 85% and 88% of the patients in each treatment group completed the study, and the duration and extent of exposure to study medication were comparable across treatment groups.

When cardiovascular-thromboembolic CRAEs were evaluated over the entire period of treatment (ie, the IV administration period and the oral administration period considered together), results from Study 93-071 confirmed the cardiovascular safety signal observed in Study 93-035 (Section 2.3.2.1): a significantly larger percentage of patients ($p = 0.033$) had cardiovascular-thromboembolic CRAEs in the parecoxib sodium/valdecoxib treatment group (11/544 patients, 2.0%) versus the placebo/placebo group (3/548 patients, 0.5%). Differences in percentages of patients with cardiovascular-thromboembolic CRAEs were not statistically significant when the placebo/valdecoxib treatment group (6/544 patients, 1.1%) was compared to the placebo/placebo treatment group.

Table 12. Cardiovascular and Renal CRAEs[a] in Coronary Artery Bypass Graft Surgery Study 93-071: IV Parecoxib Sodium and Oral Valdecoxib Dosing Periods Together

(Number [%] of Patients)

Adverse Event Category Adverse Event or Subcategory	Pbo/Pbo N = 548	Pbo/Valde N = 544	Pare/Valde N = 544	p-value, Pbo/Valde vs Pbo/Pbo	p-value, Pare/Valde vs Pbo/Pbo
Cardiovascular Thromboembolic	**3 (0.5)**	**6 (1.1)**	**11 (2.0)**	**--**	**0.033**
Myocardial[b]	**0 (0.0)**	**2 (0.4)**	**4 (0.7)**	**--**	**0.061**
Myocardial infarction	0 (0.0)	1 (0.2)	1 (0.2)	--	--
Cardiac arrest, non-resuscitated	0 (0.0)	0 (0.0)	1 (0.2)	--	--
Cardiac arrest, resuscitated	0 (0.0)	1 (0.2)	1 (0.2)	--	--
Sudden cardiac death	0 (0.0)	1 (0.2)	1 (0.2)	--	--
Stroke or transient ischemic attack[c]	**2 (0.4)**	**2 (0.4)**	**5 (0.9)**	**--**	**--**
Cardioembolic, probable	1 (0.2)	1 (0.2)	2 (0.4)	--	--
Cardioembolic, possible	1 (0.2)	0 (0.0)	0 (0.0)	--	--
Acute ischemic stroke of unknown cause	0 (0.0)	1 (0.2)	0 (0.0)	--	--
Transient ischemic attack	0 (0.0)	0 (0.0)	3 (0.6)	--	0.123
Vascular thrombosis	**1 (0.2)**	**0 (0.0)**	**0 (0.0)**	**--**	**--**
Pulmonary embolism	**1 (0.2)**	**2 (0.4)**	**2 (0.4)**	**--**	**--**
Renal Dysfunction/Failure	**3 (0.5)**	**4 (0.7)**	**7 (1.3)**	**--**	**--**
Due to need for peritoneal or hemodialysis post-surgery	0 (0.0)	2 (0.4)	2 (0.4)	--	--
Due to persistently elevated serum creatinine	3 (0.5)	2 (0.4)	5 (0.9)	--	--

Note: If a patient had more than one event within a category, that patient is counted only once in the overall adverse events total for that category.
-- Indicates p >0.20; p-values were calculated using Fisher's exact test.
IV = Intravenous; Pbo = Placebo; Pare = Parecoxib sodium 60 mg TDD on Day 1 and 40 mg total daily dose thereafter for 72 hours; Valde = Valdecoxib 40 mg total daily dose for a total treatment duration (first with parecoxib sodium and then with valdecoxib) of 10 days.

[a] All clinically relevant adverse events (CRAEs) were adjudicated by a panel of independent experts who were blinded to randomized treatment assignments.

[b] Includes cardiac arrest, non-resuscitated; cardiac arrest, resuscitated; myocardial infarction; sudden cardiac death.

[c] Includes cardioembolic, possible; cardioembolic, probable; acute ischemic stroke of unknown cause; transient ischemic attack.

When cardiovascular thromboembolic and renal dysfunction/failure CRAEs were evaluated separately for the IV and oral dosing periods in Study 93-071, no statistically significant differences were observed for either the placebo/valdecoxib treatment group or the parecoxib sodium/valdecoxib treatment group compared to the placebo/placebo treatment group (Table 13). When evaluated for the oral dosing period only, the composite CRAE endpoint, which includes gastrointestinal events and surgical wound complications in addition to cardiovascular thromboembolic events and renal dysfunction/failure events, was significantly more likely in the placebo/valdecoxib treatment group compared to the placebo/placebo treatment group. This result was driven largely by an excess of patients with surgical wound complications in the placebo/valdecoxib treatment group.

Table 13. CRAEs[a] in IV Parecoxib Sodium Versus Oral Valdecoxib Dosing Periods: Coronary Artery Bypass Graft Surgery Study 93-071

(Number [%] of Patients)

Adverse Event or Event Category	Pbo/Pbo N = 548	Pbo/Valde N = 544	Pare/Valde N = 544	p-value, Pbo/Valde vs Pbo/Pbo	p-value, Pare/Valde vs Pbo/Pbo
Any Clinically Relevant Adverse Event					
Intravenous dosing period only	5 (0.9)	10 (1.8)	13 (2.4)	-	0.061
Oral dosing period only	17 (3.4)	31 (6.2)	27 (5.3)	0.039	0.165
Any Cardiovascular Thromboembolic					
Intravenous dosing period only	1 (0.2)	3 (0.6)	4 (0.7)	-	-
Oral dosing period only	2 (0.4)	3 (0.6)	7 (1.4)	-	0.178
Myocardial[b]					
Intravenous dosing period only	0 (0.0)	2 (0.4)	1 (0.2)	-	-
Oral dosing period only	0 (0.0)	0 (0.0)	3 (0.6)	-	-
Stroke or Transient Ischemic Attack[c]					
Intravenous dosing period only	1 (0.2)	1 (0.2)	3 (0.6)	-	-
Oral dosing period only	1 (0.2)	1 (0.2)	2 (0.4)	-	-
Vascular Thrombosis					
Intravenous dosing period only	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Oral dosing period only	1 (0.2)	0 (0.0)	0 (0.0)	-	-
Pulmonary Embolism					
Intravenous dosing period only	0 (0.0)	0 (0.0)	0 (0.0)	-	-
Oral dosing period only	1 (0.2)	2 (0.4)	2 (0.4)	-	-
Renal failure/dysfunction					
Intravenous dosing period only	3 (0.5)	4 (0.7)	6 (1.1)	-	-
Oral dosing period only	0 (0.0)	0 (0.0)	1 (0.2)	-	-

Note: If a patient had more than one event within a category, that patient is counted only once in the overall adverse events total for that category.
- Indicates p >0.20 or could not be calculated; p-values were calculated using Fisher's exact test.
IV = Intravenous; Pbo = Placebo; Pare = Parecoxib sodium; Valde = Valdecoxib.

[a] All clinically relevant adverse events (CRAEs) were adjudicated by a panel of independent experts who were blinded to randomized treatment assignments.

[b] Includes cardiac arrest, non-resuscitated; cardiac arrest, resuscitated; myocardial infarction; sudden cardiac death.

[c] Includes cardioembolic, possible; cardioembolic, probable; acute ischemic stroke of unknown cause; transient ischemic attack.

2.3.3. General Surgery Study 93-069

In Study 93-069, treatment with parecoxib sodium/valdecoxib was evaluated at a dose of 40 mg TDD using a double-blind, parallel-group study design with IV treatment (parecoxib sodium or placebo) for 3 days followed by oral treatment (valdecoxib or placebo) for 7 days; patients with inadequate pain relief at any time during the study were allowed to receive supplemental opioid analgesia consistent with standard of care. Of the 1050 patients who

received study medication, 525 patients were treated with placebo/placebo and 525 patients were treated with parecoxib sodium/valdecoxib. Approximately 88% of patients in both treatment groups completed the study. The duration and extent of exposure to study medication were comparable across treatment groups, and no significant differences were observed between treatment groups in baseline demographics, vital signs, or medical histories and risk factors. Also, no significant differences between treatment groups were observed for the categories of general surgery performed (orthopedic, 27% of patients in both treatment groups; gastrointestinal, 38% for placebo and 36% for parecoxib sodium/valdecoxib; gynecologic, 20% for placebo and 19% for parecoxib sodium/valdecoxib; thoracic, 2% for both treatment groups; and other, 18% for placebo and 20 % for parecoxib sodium/valdecoxib) or for the details of surgical procedures. The mean patient ages in Study 93-069 were 53-54 years across treatment groups, approximately 40% of patients were males, and more than 90% of the patients in each treatment group were white.

When cardiovascular thromboembolic CRAEs were evaluated in Study 93-069 for the entire period of treatment (ie, the IV administration period and the oral administration period considered together), no statistically significant differences were observed between the parecoxib sodium/valdecoxib 40 mg TDD treatment group and the placebo/placebo treatment group (Table 14).

Table 14. Cardiovascular and Renal CRAEs[a] in General Surgery Study 93-069: IV Parecoxib Sodium and Oral Valdecoxib Dosing Periods Together

(Number [%] of Patients)

Adverse Event Category Adverse Event	Placebo/ Placebo N = 525	Parecoxib Sodium/Valdecoxib N = 525	p-value
Cardiovascular Thromboembolic	**5 (1.0)**	**5 (1.0)**	-
Myocardial infarction	0 (0.0)	2 (0.4)	-
Cardiac arrest or sudden cardiac death	1 (0.2)	1 (0.2)	-
Acute ischemic stroke	1 (0.2)	0 (0.0)	-
Deep vein thrombosis	2 (0.4)	1 (0.2)	-
Pulmonary embolism	1 (0.2)	1 (0.2)	-
Renal	**0 (0.0)**	**1 (0.2)**	**-**
Renal failure/dysfunction	0 (0.0)	1 (0.2)	-

Note: If a patient had more than one event within a category, that patient is counted only once in the overall adverse events total for that category.
IV = Intravenous.
- Indicates p >0.20; p-values were calculated using Fisher's exact test.
[a] All clinically relevant adverse events (CRAEs) were adjudicated by a panel of independent experts who were blinded to randomized treatment assignments.

When cardiovascular thromboembolic and renal failure/dysfunction CRAEs were evaluated separately for the IV and oral dosing periods in Study 93-069, no differences were observed for the parecoxib sodium/valdecoxib treatment group compared to the placebo/placebo treatment group (Table 15).

Table 15. CRAEs[a] in IV Parecoxib Sodium Versus Oral Valdecoxib Dosing Periods: General Surgery Study 93-069

(Number [%] of Patients)

Adverse Event or Event Category	Placebo/ Placebo N = 525	Parecoxib Sodium/ Valdecoxib N = 525	p-value
Any Clinically Relevant Adverse Event			
Intravenous dosing period only	6 (1.1)	3 (0.6)	-
Oral dosing period only	11 (2.1)	11 (2.1)	-
Any Cardiovascular Thromboembolic			
Intravenous dosing period only	1 (0.2)	2 (0.4)	-
Oral dosing period only	4 (0.8)	3 (0.6)	-
Myocardial infarction			-
Intravenous dosing period only	0 (0.0)	1 (0.2)	-
Oral dosing period only	0 (0.0)	1 (0.2)	-
Cardiac arrest or sudden cardiac death			-
Intravenous dosing period only	1 (0.2)	0 (0.0)	-
Oral dosing period only	0 (0.0)	1 (0.2)	-
Acute Ischemic Stroke of Unknown Cause			
Intravenous dosing period only	0 (0.0)	0 (0.0)	-
Oral dosing period only	1 (0.2)	0 (0.0)	-
Deep vein thrombosis			
Intravenous dosing period only	0 (0.0)	0 (0.0)	-
Oral dosing period only	2 (0.4)	1 (0.2)	-
Pulmonary embolism			-
Intravenous dosing period only	0 (0.0)	1 (0.2)	-
Oral dosing period only	1 (0.2)	0 (0.0)	-
Renal failure/dysfunction			-
Intravenous dosing period only	0 (0.0)	1 (0.2)	-
Oral dosing period only	0 (0.0)	0 (0.0)	-

Note: If a patient had more than one event within a category, that patient is counted only once in the overall adverse events total for that category.
IV = Intravenous.
- Indicates p >0.20 or could not be calculated; p-values were calculated using Fisher's exact test.
[a] All clinically relevant adverse events (CRAEs) were adjudicated by a panel of independent experts who were blinded to randomized treatment assignments.

These results, which show no cardiovascular safety signal in general surgery patients, suggest the hypothesis that the increased cardiovascular risk observed for patients treated with parecoxib sodium/valdecoxib in Studies 93-035 and 93-071 is limited to the setting of post-CABG surgery, ie, procedures involving coronary bypass in high risk cardiovascular patients, but not general surgery patients undergoing major abdominal and orthopedic procedures. This hypothesis is further confirmed by the post hoc analysis described below.

2.3.4. Post Hoc Analysis of Clinically Relevant Adverse Events (CRAEs): Integrated Data From General Surgery Studies

The CRAE analyses from Studies 93-069 and 93-071 provided data on specially designated categories of adjudicated adverse events. In these studies, analysis of composite CRAEs (including cardiovascular thromboembolic CRAEs, together with other CRAEs relevant to surgery patients) constituted the primary evaluation of parecoxib sodium and valdecoxib safety. To evaluate the incidence with valdecoxib in general surgery patients of events resembling these CRAEs, Pfizer undertook a post-hoc analysis of integrated data from 17 general surgery and ankle sprain studies using valdecoxib 20-60 mg TDD (listed in Table 16). Together these 17 studies represent the entire valdecoxib general surgery (ie, non-CABG surgery) database for treatment with valdecoxib at all doses approved in Canada. Hence, this post-hoc analysis excludes CABG Surgery Studies 93-035 and 93-071, as well as General Surgery Study 072, in which all patients received valdecoxib 80 mg TDD (a dose in excess of the approved valdecoxib doses for OA and RA in Canada). Adverse events were summarized for categorization in this post hoc analysis as follows:

- First, WHOART preferred adverse event terms were matched as closely as possible, using best clinical judgment, to the definitions of CRAEs prespecified for Studies 93-069, and 93-071.

- Second, analyses of the specific groupings of adverse event terms identified above were compared with corresponding analyses of CRAEs from Studies 93-069, and 93-071 to confirm that both analyses yielded similar safety conclusions.

- Confirmation that the CRAE and matching WHOART preferred term analyses described above yielded similar safety conclusions validated the hypothesis that matching WHOART preferred terms could be used post hoc to evaluate the integrated dataset from 17 general surgery studies in a manner analogous to the CRAE analyses in Studies 93-069 and 93-071.

Integrated data from 17 valdecoxib general surgery studies and ankle sprain studies, evaluated for CRAE-matching WHOART preferred adverse event terms as described above, indicated no significant differences between the valdecoxib 20-60 mg TDD treatment group and the placebo treatment group (Table 17). Therefore, safety concerns identified in the CABG surgery patient population are not characteristic of the broader surgery/ankle sprain patient population.

Table 16. Valdecoxib Surgery and Ankle Sprain Studies Integrated for Analysis

Study Type	Study ID	Short Description (dose, duration, population)
Orthopedic Surgery	032	Valdecoxib 20 mg PO or valdecoxib 40 mg PO on Day 1 followed by valdecoxib 20 mg PO or valdecoxib 40 mg PO q4-6h PRN on Days 2-4, adult males and females for orthopedic total hip arthroplasty
	037	Single PO dose of valdecoxib 20, 40, or 80 mg, adult males and females for bunionectomy surgery
	038	Valdecoxib 20 mg BID or valdecoxib 40 mg BID (single postoperative dose followed by dose q12h for up to 48 hours), adult males and females for unilateral knee arthroplasty surgery
	051	Valdecoxib 20 mg BID or valdecoxib 40 mg BID (single preoperative dose followed by dose q12h for up to 48 hours), adult males and females for primary hip arthroplasty
	081	Single PO dose of valdecoxib 40 mg, adult males and females for bunionectomy surgery
	110	Valdecoxib 40 mg PO QD with optional single redose of valdecoxib 40 mg PO on Day 1 followed by valdecoxib 40 mg PO QD on Days 2-7, adult males and females for anterior cruciate ligament reconstruction surgery
	144	Valdecoxib 40 mg PO followed by valdecoxib 20 mg PO within 1-12 hours on Day 1 and Days 2-5 valdecoxib 20 mg BID PO or valdecoxib 20 mg QD PO, adult males and females for bunionectomy surgery
	149	Valdecoxib 40 mg PO followed by valdecoxib 20 mg PO or valdecoxib 40 mg PO followed by placebo, 24 hours, adult males and females for bunionectomy surgery
Gynecologic Surgery	011	Single PO dose of valdecoxib 20 mg or 40 mg on Day 1 followed by Days 2-4 dosing of valdecoxib 20 mg PO Q4-6h PRN or valdecoxib 10 mg PO Q4-6h PRN, adult females for elective hysterectomy or a myomectomy
	033	Single PO dose of valdecoxib 10 mg or 20 mg or 40 mg, adult females for elective hysterectomy or a myomectomy
	084	Single PO dose of valdecoxib 20 mg or valdecoxib 40 mg, adult females for elective lower abdominal gynecologic surgery
General Surgery	010	Single PO dose of valdecoxib 10 mg or 20 mg on Day 1 followed by Days 2-7 dosing Q4-6h PRN of valdecoxib 10 mg PO or valdecoxib 20 mg PO, adult males and females following major surgery
	052	Valdecoxib 20 mg BID PO or valdecoxib 40 mg BID PO for 36 hours, adult males and females for inguinal hernia repair surgery
	93-044	Single preoperative dose of parecoxib sodium 40 mg IV on Day 1, followed by valdecoxib 40 mg PO 6-12 hours after parecoxib, then valdecoxib 40 mg PO every AM on Days 1-4 and valdecoxib 40 mg PO daily PRN for Days 5-7, males or females for elective laparoscopic cholecystectomy surgery
	93-069	Parecoxib sodium 40 mg IV followed by 20 mg IV every 12 hours up to 72 hours through at least Day 3 followed by valdecoxib 20 mg q12h through Day 10, adult males and females for major orthopedic or general surgery
	145	Valdecoxib 40 mg PO followed by valdecoxib 20 mg PO on Day 1, then valdecoxib 20 mg PO BID or valdecoxib 20 mg PO QD on Days 2-5, adult males and females for laparoscopic cholecystectomy surgery
Ankle Sprain	IFL-0513-008	Valdecoxib 40 mg PO loading dose followed by valdecoxib 20 mg PO QD or 20 mg PO BID for 7 days, adult male and females with lateral ankle sprain

BID = Twice daily; CABG = Coronary artery bypass graft; h = Hour; IM = Intramuscular; IV = Intravenous; PRN= As needed; PO = By mouth (oral); OA = Osteoarthritis; q12h = Every 12 hours; QD = Once daily; TDD = Total daily dose.

Table 17. Analysis of Selected Cardiovascular and Renal Adverse Events Based on Matching CRAE Definitions: General Surgery/Ankle Sprain Studies[a] With a Valdecoxib 20-60 mg Total Daily Dose Group

(Number [%] of Patients)

Adverse Event Category Adverse Event[b]	Adverse Events Placebo N = 1965	 Valde N = 3076	 p-value	Serious Adverse Events Placebo N = 1965	 Valde N = 3076	 p-value
Any Event	**34 (1.7)**	**41 (1.3)**	**--**	**15 (0.8)**	**15 (0.5)**	**--**
Any Cardiovascular Event	**9 (0.5)**	**6 (0.2)**	**0.114**	**8 (0.4)**	**5 (0.2)**	**0.151**
Myocardial	1 (<0.1)	1 (<0.1)	--	1 (<0.1)	1 (<0.1)	--
Cerebrovascular	2 (0.1)	1 (<0.1)	--	2 (0.1)	1 (<0.1)	--
Deep vein thrombosis	5 (0.3)	3 (<0.1)	--	4 (0.2)	2 (<0.1)	--
Pulmonary embolism	2 (0.1)	2 (<0.1)	--	2 (0.1)	2 (<0.1)	--
Any Renal Event	**1 (<0.1)**	**3 (<0.1)**	**--**	**0 (0.0)**	**2 (<0.1)**	**--**

-- Indicates p >0.20; p-values were calculated using Fisher's exact test.
CRAE = Clinically relevant adverse event; Valde = Valdecoxib 20-60 mg total daily dose.

[a] Includes all studies listed in Table 16 except Studies 93-035, 93-071, and 072; for Study 93-044, in which patients received first intravenous parecoxib sodium and then oral valdecoxib, only events that occurred during the oral valdecoxib dosing period/28-day follow-up are included.

[b] Adverse events summarized in this table were identified post hoc using WHOART preferred terms that matched as closely as possible, using best clinical judgment, the clinically relevant adverse events (CRAEs) prespecified for Studies 93-069, and 93-071.

2.4. Cardivoascular Safety in Clinical Studies in the Medical Literature

Other than the increased cardiovascular safety risk observed with parecoxib sodium/valdecoxib treatment in CABG surgery patients in Study 93-035 and Study 93-071 (described in Section 2.3), no indication of any cardiovascular safety signal for valdecoxib appears in the published medical literature, including a meta-analysis of data from 10 valdecoxib clinical trials representing nearly 8000 OA and RA patients with treatment up to 1 year in duration (most patients were treated with valdecoxib in studies with up to 3 months duration).

2.4.1. Valdecoxib Studies in Chronic Indications

To date, there have been no valdecoxib clinical trials longer than 1 year in duration. In a recently published meta-analysis of data from 10 valdecoxib clinical trials representing nearly 8000 OA and RA patients, including over 4500 patients who took valdecoxib 10-80 mg QD for up to 1 year (most patients were treated with valdecoxib in studies with up to 3 months duration), there were no significant differences in exposure-adjusted event rates when cardiovascular serious adverse events (defined as treatment-emergent acute myocardial infarction, stroke, deep vein thrombosis, pulmonary embolism, or peripheral arterial thrombosis considered serious by investigators and adjudicated by the authors of the study) were compared for patients who received valdecoxib versus patients who received placebo or non-selective NSAIDs; also, no differences were observed for composite cardiovascular serious adverse events or individually for myocardial infarction or stroke when data were stratified for aspirin use versus no aspirin use.[15] These conclusions are consistent with those of the larger meta-analysis presented in Section 2.2.

Published reports of individual clinical studies in chronic indications generally report comparable efficacy for valdecoxib relative to naproxen or diclofenac and significantly better efficacy than placebo, with no cardiovascular safety signals.

2.4.2. Valdecoxib General Surgery Studies

A systematic review of published clinical trials reporting treatment with valdecoxib for post-operative pain indicates efficacy comparable to that of rofecoxib and nonselective NSAIDs and reports no cardiovascular safety signal.[21] This systematic review, like the meta-analysis of data from chronic pain studies described above,[15] did not include studies in which CABG surgery patients were treated with parecoxib sodium/valdecoxib (described in Section 2.3). Pfizer contends that it is inappropriate and misleading to include cardiovascular safety data from parecoxib sodium/valdecoxib clinical trials in CABG patients together with cardiovascular safety data from valdecoxib clinical trials in arthritis patients in a meta-analysis to evaluate the overall benefit/risk of valdecoxib, in the manner recently reported by FitzGerald.[22]

Published reports of individual clinical studies in various surgical settings generally indicate comparable efficacy for valdecoxib[23,24] or parecoxib sodium/valdecoxib[25,26] relative to active comparators, or significant opioid sparing, with no apparent cardiovascular safety signals; the two exceptions are publications that report the results of Study 93-035 and Study 93-071 in

CABG surgery patients (see Section 2.3), including the observation of a potential cardiovascular safety signal associated with parecoxib sodium/valdecoxib treatment in this unique, high-risk patient population.[27,28] Additionally, a single, small study (98 patients total) of post-operative naproxen use compared to placebo after CABG surgery has been published;[29] this publication did not report results for cardiovascular adverse events and is therefore not helpful for placing cardiovascular safety data from parecoxib sodium/valdecoxib in clinical context.

2.5. Spontaneous Reports of Cardiovascular Adverse Events With Valdecoxib

Although it historically represents the least precise method for evaluation of cardiovascular risk, analysis of spontaneous reports shows results consistent with both randomized clinical trial data and epidemiology data indicating no increase in cardiovascular risk with valdecoxib.

2.5.1. Methods for Analysis

Pfizer's early alert safety database contains cases of adverse events reported spontaneously to Pfizer, cases reported from health authorities, cases published in the medical literature, and cases of serious adverse events reported from clinical studies and Pfizer-sponsored marketing programs (solicited cases) regardless of causality. For this review the database was searched for all valdcoxib non-clinical study cases reported from 1 November 2001 through 31 October 2004.

The database was further searched to identify valdecoxib cases reporting thrombotic events (including events suggestive of coronary artery disease or thromboembolism or occlusion, cardiac ischemia, myocardial infarction, or arrhythmia events likely to be associated with coronary thromboembolism or ischemia; cerebrovascular thromboembolism or occlusion or ischemia or infarction, cerebrovascular hemorrhage, or neurologic events likely to be associated with cerebrovascular ischemia or hemorrhage; non-coronary or non-cerebrovascular thromboemolism, occlusion, ischemia, or infarction) and cardiorenal events (events suggestive of hypertension, abnormal or fluctuating or inadequately controlled or increased blood pressure, cardiac failure, or edema events possible related to hypertension or cardiac failure). Cases identified by these searches were then further reviewed to characterize the nature of any cardiovascular risk factors present.

In addition, in an effort to compare information on the reporting of these types of adverse events for COX-2 inhibitors and the conventional non-selective NSAIDs, the FDA's Adverse Event Reporting System (AERS) database available under the Freedom of Information Act was reviewed using Drug Logic's QScan (version 3.0) for information on adverse events reported to FDA for the COX-2 inhibitors valdecoxib and rofecoxib, and for the conventional NSAIDs diclofenac, ibuprofen, naproxen, and piroxicam using the same search strategy that was employed to search for valdcoxib cases in Pfizer's database.

2.5.2. Results: Spontaneous Reports of Cardiovascular Adverse Events for Valdecoxib

Review of Pfizer's early alert safety database identified a total of 13,924 valdecoxib non-clinical study cases reported through 31 October 2004 following treatment of approximately 13.5 million patients worldwide. Of these, there were 138 cases reporting thrombotic events (of which 72 reported cardiac events, 49 reported cerebrovascular events, and 20 reported peripheral vascular events; 111 of these 138 cases met the reporting criteria for a serious case, and deaths were reported in 16 of these 111 serious cases) and 1,142 cases reporting cardiorenal events (198 of these 1142 cases met the reporting criteria for a serious case, and deaths were reported in 3 of these 198 serious cases). When the reporting of these events for valdecoxib to the FDA's AERS system was compared to the reporting of these events for rofecoxib, diclofenac, ibuprofen,

naproxen, and piroxicam, the proportion of cases reporting these events was generally greatest for rofecoxib, and the proportion of valdecoxib cases reporting these events was generally similar to the proportion of diclofenac cases reporting these events.

For valdecoxib cases reported to Pfizer, the cases reporting cardiac events, cerebrovascular events, and all thrombotic events had a greater proportion of elderly and male patients, suggesting a patient population generally already at elevated cardiovascular risk. Cases reporting these events were also more likely to have reported concomitant medications and information concerning medical history than were all valdecoxib cases, also suggesting that these cases involved patients at greater risk of adverse events. Review of the data for daily dose of valdecoxib identified no suggestion of increased risk for any of the event categories reviewed with increased dose. For cardiac, cerebrovascular, peripheral vascular, and all thrombotic events, the most commonly reported durations of therapy at event onset were ≤ 1 day and 8 days-6 months. For cases reporting cardiorenal events, the distribution of cases reporting duration of therapy at onset of the first events was similar to that of all valdecoxib non-clinical study cases. Interpretation of these data is made difficult by the fact that duration of use was unknown or not reported in more than half of the cases for all event categories reviewed. There was no apparent association between any of the event categories reviewed and concurrent aspirin therapy.

Cases where the patient was reported to have died for all event categories reviewed had a greater proportion of elderly patients than did all valdecoxib non-clinical study cases and all cases for the corresponding event categories. Cases reporting hypertension were no more likely to have reported concurrent cardiac or cerebrovascular events than were all valdecoxib non-clinical study cases, and it is unclear if such events are independent of hypertension in valdecoxib-treated patients or if hypertension-related events are underreported in valdecoxib cases reporting cardiac and/or cerebrovascular events.

Overall, this review of valdecoxib non-clinical study cases did not identify any signal indicating that valdecoxib therapy increases risk of cardiac, cerebrovascular, peripheral vascular, thrombotic, or cardiorenal adverse events independent of the risk inherent in the patient population likely to be treated with valdecoxib.

2.6. Conclusions, Valdecoxib Cardiovascular Safety

Data presented and reviewed in this evaluation of valdecoxib cardiovascular safety support the following conclusions:

- A meta-analysis of cardiovascular safety data from randomized clinical trials representing a total of 7061 patients with chronic pain conditions treated with valdecoxib at doses ranging from 1 to 80 mg TDD for durations ranging from 2 weeks to 1 year (most patients were treated with valdecoxib in studies with up to 3 months duration) shows no significant increase in cardiovascular thromboembolic risk for valdecoxib compared to nonselective NSAIDs or placebo (Section 2.2). However, due to limited exposure to study medication and small numbers of events, comparisons between valdecoxib and nonselective NSAIDs or placebo are of very limited value for the statistical evaluation of cardiovascular effects.

- An increase in cardiovascular adverse events was observed with sequential parecoxib sodium/valdecoxib treatment compared to placebo treatment with exposure for up to 14 days in CABG Surgery Studies 93-035 and 93-071 (Section 2.3). CABG surgery patients represent a high-risk population due to cardiopulmonary bypass procedures and the resulting potential for a unique and highly dynamic pro-thrombotic and inflammatory syndrome. As a result, the use of parecoxib sodium or valdecoxib in the post-CABG surgery setting is contraindicated. No increases in cardiovascular adverse events were observed in any other post-surgical setting (Sections 2.3.3 and 2.3.4). However, valdecoxib safety has not been evaluated in other revascularization procedures.

- Postmarketing safety surveillance representing a total of 13,924 valdecoxib non-clinical study cases reported through 31 October 2004 following treatment of approximately 13.5 million patients worldwide does not show a cardiovascular safety signal for valdecoxib (Section 2.5).

The cumulative data presented and reviewed in this Briefing Document suggest that valdecoxib is safe and well tolerated when used as directed, presenting a cardiovascular risk profile comparable to that of nonselective NSAIDs, the most prominent alternatives for treatment of arthritis. Longer-term data and epidemiologic studies are required, however, to enhance the valdecoxib cardiovascular safety database, which is currently more limited than for celecoxib.

3. PLANS FOR FURTHER EVALUATION OF CARDIOVASCULAR SAFETY

3.1. Prospective Clinical Studies

Pfizer believes it is currently premature to consider the design of a valdecoxib cardiovascular safety study, since the regulatory position of the drug remains unclear and sales are currently suspended in major markets. If valdecoxib is re-introduced to major markets, however, a long-term cardiovascular events trial would answer critical questions regarding the long-term cardiovascular safety of valdecoxib.

3.2. Epidemiological Studies

Epidemiological studies either fully sponsored by Pfizer or partially funded by independent research grants (IRGs), currently ongoing with valdecoxib included among the prespecified investigational study drugs, are summarized below. The main characteristics of each study and corresponding timelines are presented in Table 18.

1. **Risk of acute myocardial infarction in users of valdecoxib and other COX-2 specific inhibitors in Medicare, US (IRG).**
   Principal investigator: Solomon DH, Harvard Medical School
   Final report 3Q05-Manuscript 4Q05

   Retrospective cohort study conducted in the Pennsylvania and New Jersey Medicare populations to estimate the risk of cardiovascular (acute myocardial infarction and coronary death) and cerebrovascular events (ischemic stroke) associated with the use of COX-2 specific inhibitors, including valdecoxib, celecoxib, rofecoxib, and non-selective NSAIDS, during the years 2002 and 2003. The exposure assessment will be studied for low and high doses and for current and past users. Effects of confounders such as use of over-the-counter NSAIDs and aspirin, body mass index, smoking, and socio-economic status will be estimated from the 2002 Medicare Current Beneficiary Survey. Cases are identified using ICD-9 codes from Hospital Discharge Services and Vital Statistics. Case validation will not be conducted as prior studies in this population have shown a positive predictive value of 93% for ICD-9 code 410 (acute myocardial infarction).

2. **Risk of acute myocardial infarction in patients with osteoarthritis and rheumatoid arthritis in MediCal, US (IRG).**
   Principal investigator: Singh G, Stanford University
   Final report/manuscript 3Q05

   Nested case-control study conducted in the MediCal Healthcare System population to estimate the risk of acute myocardial infarction associated with the use of COX-2 specific inhibitors, valdecoxib, celecoxib, rofecoxib, and non-selective NSAIDS, in patients aged 18 to 84 years with arthritis (OA/RA) and/or musculoskeletal disorders from January 1, 1999 to June 30, 2004. The study will assess the effect of dose, use of over-the-counter NSAIDs and aspirin, and of other risk factors. Cases are identified using ICD-9 codes from reimbursement records. There is no case validation conducted in this study.

3. **Risk of cerebrovascular events associated with the use of COX-2 inhibitors in Medicaid Tennessee, US.**
   Principal investigator: Griffin M, Vanderbilt University
   Final report/manuscript 2Q06

   Retrospective cohort study conducted in the Medicaid Tennessee population aged 50 to 84 years old to assess the risk of cerebrovascular diseases (ischemic and hemorrhagic stroke) associated with the use of COX-2 specific inhibitors (valdecoxib, celecoxib, rofecoxib, and non-selective NSAIDS), between January 1, 1999 and June 30, 2003. Cases will be identified using ICD-9 codes from Hospital Discharge Services and Vital Statistics. A random sample of 100 cases will be validated through review of medical charts.

Table 18. Summary of Ongoing Cardiovascular Epidemiological Studies Involving Valdecoxib Sponsored by Pfizer or Partially Funded by Independent Research Grants From Pfizer

Study and setting	Principal investigator	Study design	Study drugs	Final report/manuscript
Risk of AMI, coronary death, and ischemic stroke *Medicare Pennsylvania-New Jersey, US*	Solomon DH *Harvard Medical School*	Cohort	valdecoxib celecoxib rofecoxib NSAIDs	Report 3Q05 Manuscript 4Q05
Risk of AMI in an OA-RA population *MediCal (California Medicaid), US*	Singh G *Stanford University*	Nested case-control	valdecoxib celecoxib rofecoxib NSAIDs	3Q05
Risk of stroke *Medicaid Tennessee, US*	Griffin M *Vanderbilt University*	Cohort	valdecoxib celecoxib rofecoxib NSAIDs	2Q06

AMI = Acute myocardial infarction; OA = Osteoarthritis; RA = Rheumatoid arthritis.

4. SKIN REACTIONS WITH VALDECOXIB

4.1. Overall Conclusions

Safety analysis of serious skin reactions based on data from clinical studies, epidemiological studies, and spontaneous reports indicates that the reporting rate of SCAR with valdecoxib is several-fold higher than that observed with other selective COX-2 inhibitors, and is only marginally worse than the rates observed with some nonselective NSAIDs, and is generally lower than rates observed with anti-epileptic agents. Therefore, in addition to actions already taken over the past 2 years as part of a program to further reduce risk, Pfizer proposes a series of risk management actions to enable the resumption of sales and marketing/availability of valdecoxib for OA and RA patients in the context of information adequate for risk/benefit considerations in individual patients. Collectively it is estimated that these actions would reduce the risk of fatal SCAR reactions several-fold, bringing the rates of SCAR-related fatalities and irreversible sequelae more in line with those of other anti-inflammatory agents.

- Amend the valdecoxib prescribing information to limit the indicated use of valdecoxib in OA and RA to patients who have failed to respond to or could not tolerate nonselective NSAIDs and other selective COX-2 inhibitors. This would reduce total usage (and assure it is in a setting where a specific benefit offsets the risk) and hence would reduce the total number of SCAR cases.

- Because dosage is a risk factor for SCAR and because the risk may be similar or increased with each recurrent use, remove the indication for valdecoxib in primary dysmenorrhea. This indication requires the highest daily dose and typically calls for intermittent use of valdecoxib that could possibly expose the user to repeated cycles of high initial therapy risk.

- Because 90% of the documented cases with valdecoxib occur within the first 3 weeks of therapy and epidemiologic studies show a marked decrease in risk after several weeks of therapy; and because prompt withdrawal of the offending agent is the most effective treatment for SCAR, it is proposed that there be more frequent and intense monitoring of patients taking valdecoxib during this initial period. In addition, prescribing information and patient/physician education materials will stress the importance of immediate discontinuation of valdecoxib and notification to the treating physician at the first evidence of dermal and/or mucosal signs or symptoms, especially during the first month of therapy. Pfizer will work with regulatory agencies in Canada and elsewhere to develop programs to assure compliance with these measures.

4.2. Background

Although pharmaceutical agents can induce a variety of immunological responses, the majority of drug hypersensitivity reactions are immunoglobulin-E, or T-cell-mediated reactions. These are often complex reactions in which allergic and non-allergic mechanisms co-exist; they are difficult to predict and their diagnosis is frequently obscured by the involvement of a direct

pharmacological effect of the administered drug. The acronym SCAR encompasses a series of related severe cutaneous adverse drug reactions, believed to be T-cell mediated delayed hypersensitivity reactions. Internationally, there is now close agreement among authors on the conditions that are covered by this term:

- Erythema multiforme (EM),
- Stevens-Johnson syndrome (SJS),
- Toxic epidermal necrolysis (TEN), also known as Lyell's syndrome.

However, there is still no consistent agreement on differential diagnoses among these three conditions; in particular, differentiation between TEN and SJS and between SJS and EM is problematic. For this reason, there has never been a fully uniform terminology to describe these conditions,[30] and furthermore, it should be noted that exfoliative dermatitis is often incorrectly included in this classification. The most widely used classification of SCAR (Table 19), developed by Bastuji-Garin,[31] differentiates among the various conditions according to the degree of epidermal detachment and the type and body distribution of lesions. This classification will be used to define SCAR in these responses (except where indicated otherwise).

Among the three conditions in the SCAR continuum, SJS and TEN are the two diagnoses associated with a significant degree of mortality. Depending on the authors, the estimated mortality rates for SJS range from 4% to 7%, and could be as high as 35-45% for "full blown" cases of TEN. In contrast, EM is only associated with a limited mortality rate (estimated around 1%), mostly in cases considered to be "EM/SJS transitional".[32]

Table 19. Classification of Severe Cutaneous Adverse Reactions[a]

Classification	Epidermal Detachment	Type of Lesions	Distribution of Lesions	Estimated Mortality[b]
EM	<10%	Typical targets[c] or raised atypical targets[d]	Localized on limbs	1%
SJS	<10%	Erythematous or purpuric macules or flat atypical targets	Widespread	4%
SJS/TEN	10-29%	Erythematous or purpuric macules or flat atypical targets	Widespread	7%
TEN with macules	>29%	Erythematous or purpuric macules or flat atypical targets	Widespread	45%[e]
TEN (pure plaque)	>29%	Large epidermal sheets without purpuric macules or targets	Widespread	45%[e]

[a] Adapted from Bastuji-Guerin et al.[31]
[b] Adapted from Auquier-Dunant et al.[32]
[c] Typical targets = round lesions less than 3cm in diameter, with 3 defined zones, ie 2 concentric rings around a central disk.
[d] Atypical targets = round edematous palpable lesions, but with only 2 zones and/or an ill-defined border.
[e] No distinction was made amongst TEN subtypes in Auquier-Dunant et al.[32]

4.2.1. Incidence of Severe Cutaneous Adverse Reactions (SCAR)

General population estimates of the incidence SJS, TEN and/or EM range from 0.4 to 7.4 cases per million persons per year.[33,34] The drug antecedent rate for SJS or TEN, as determined in a retrospective cohort study,[34] was 1.8 per million person years; few other studies clearly separate background rates from antecedent drug history. While infection and autoimmune disease have been implicated as causes of SJS/TEN,[35] drugs either alone or in combination with these conditions appear to be the most prevalent cause of SCAR and are implicated in 65% of cases.[36] More than 100 drugs have been implicated in case reports as causes of the syndrome.[30] Drugs most closely linked to SJS/TEN include sulfonamides, particularly sulfonamide antibiotics (with an arylamine group as part of the sulfonamide moiety in the para position), anticonvulsants, and NSAIDs, among others.

The relative risks of SJS/TEN associated with various drugs compared to non-use were evaluated in a European case-control study by Roujeau et al,[30] in which cases were validated by an international group of dermatologists using strict diagnostic criteria in a standardized review of all relevant clinical information. In this study, sulfonamide antibiotics were found to carry relative risks of over 100, anticonvulsants such as phenobarbital and carbamazepine had relative risks of 15 and 11, respectively, and oxicam NSAIDs were found to have a relative risk of 18. Other NSAIDs carried lower risks (eg, propionic acid NSAIDs = 4.5, diclofenac = 2.6), as did other sulfonamide-containing compounds such as thiazide diuretics (relative risk 1.9). The same authors calculated attributable risk for these classes of drug where possible, and found 4.3 excess cases per million users per week for trimethoprim-sulfamethoxazole, 2.5 excess cases per million users per week for carbamazepine, and 2.0 excess cases per million users per week for oxicam NSAIDs. Although this study predates the introduction of selective COX-2 inhibitors, it establishes the overall rarity of the syndrome yet is able to discern a range of risks among various classes of medications and, to a smaller degree, a range within each class. It is in this framework that an attempt will be made to place valdecoxib, using several methodologies as outlined below.

4.2.2. Risk Factors for Severe Cutaneous Adverse Reactions (SCAR)

Some studies have attempted to characterize risk factors for the occurrence of SCAR or other hypersensitivity reactions in the presence of drug use. One such factor is dose. The significance of a dose-response relationship for hypersensitivity reactions is demonstrated by the findings that in general, drugs administered at doses higher than 10 mg are more likely to produce hypersensitivity reactions.[37,38] A good example of how the dose can affect the incidence of severe skin rashes is with lamotrigine. A retrospective study of cases of lamotrigine-induced serious skin rashes (rash with systemic symptoms, Stevens-Johnson syndrome, erythema multiforme) in the United Kingdom (UK) showed that 11 of 12 patients with the severe skin reactions had been administered doses higher than the recommended dose and were also co-administered valproate.[39] Valproate has been shown to decrease lamotrigine metabolism and therefore increase lamotrigine exposure.

As a corollary to dose considerations, continued drug administration after first evidence of a severe cutaneous allergic reaction and/or agents with a long metabolic half-life were shown to be associated with significantly elevated mortality risk from SJS or TEN based upon a 10-year

retrospective observational study by Garcia-Doval and colleagues.[40] When drugs with short half-lives (less than 24 hours) were promptly withdrawn, mortality was significantly reduced by over 5-fold (26% vs 5%). The authors concluded that prompt withdrawal of agents should be a priority at first sign of a skin reaction.

Duration of treatment is also a significant consideration with regard to SCAR risk. Roujeau and coworkers observed that patients who had recently started therapy with any of a variety of classes of drugs had much higher risk (often ten-fold elevated) of developing SCAR during the first two months of therapy compared with longer term use.[30] Likewise, Mockenhaupt and coworkers reported that 90% of such cases occurred in the first 63 days of use of anti-epileptic medications.[41] It remains unclear whether the risk of SCAR is increased, decreased, or the same with each new course of therapy after a hiatus in treatment, and this probably depends on a variety of factors including dose and duration of therapy during the prior course, duration of the initial course of therapy, duration of the hiatus, dose on resumption, and probably many host immunologic factors as well.

Recent data from the EuroSCAR study suggest that rheumatic diseases are associated with an increased risk of SJS/TEN.[42] The overall crude relative risk relative to patients not carrying such a diagnosis for these conditions in EuroSCAR was 6.1 (95% Confidence Interval [CI]: 3.9 to 9.6). After controlling for a number of factors including use of NSAIDs, oral corticosteroids, and other "high risk" drugs, the adjusted relative risk was 5.4 (95% CI: 2.9 to 10.0). This suggests that rheumatic conditions are an independent risk factor for SJS-TEN, although residual confounding cannot be ruled out. Stimulation of innate and acquired immune systems, eg, during generalized viral infection with HIV or Epstein-Barr virus, or during acute exacerbation of autoimmune disease (eg, lupus), may provide sufficient "bystander" stimulation for an immune response to drugs as well.[43] Finally, T-cell cross reactivity puts a patient at higher risk to have a hypersensitivity reaction to drugs of a certain chemical class if the patient has had a previous reaction to another drug in the same class.[43] Although such cross-reactivity has not been demonstrated by *in vitro* techniques between classes of drugs, it would be prudent to consider patients who have already had a delayed type hypersensitivity reaction to one drug to be at higher risk to have such a reaction to another.

4.3. Severe Cutaneous Adverse Reactions (SCAR) With Valdecoxib: Clinical Studies

Because of the rare occurrence of SCAR, clinical trial databases, however large, are unlikely to provide clear estimates of the incidence of these drug reactions. Furthermore, the Pfizer serious adverse events databases (ARGUS and ARISg) do not contain a complete accounting of serious adverse events associated with placebo or comparator treatment, so there is no basis for comparison of the selective COX-2 inhibitors versus these other agents. Pfizer has examined its serious adverse events databases (ARGUS and ARISg) for SCAR with valdecoxib and parecoxib sodium, with the following results: Among approximately 20,500 patients exposed to valdecoxib in prospective clinical studies and approximately 49,500 patients exposed to valdecoxib in observational studies, there have been no reports of SCAR. Among approximately 7,700 patients exposed to the parecoxib sodium in prospective clinical studies, there have been no reports of SCAR, and there were no serious skin-related adverse events or SCAR events reported in any of the approximately 15,800 patients treated with parecoxib sodium in the

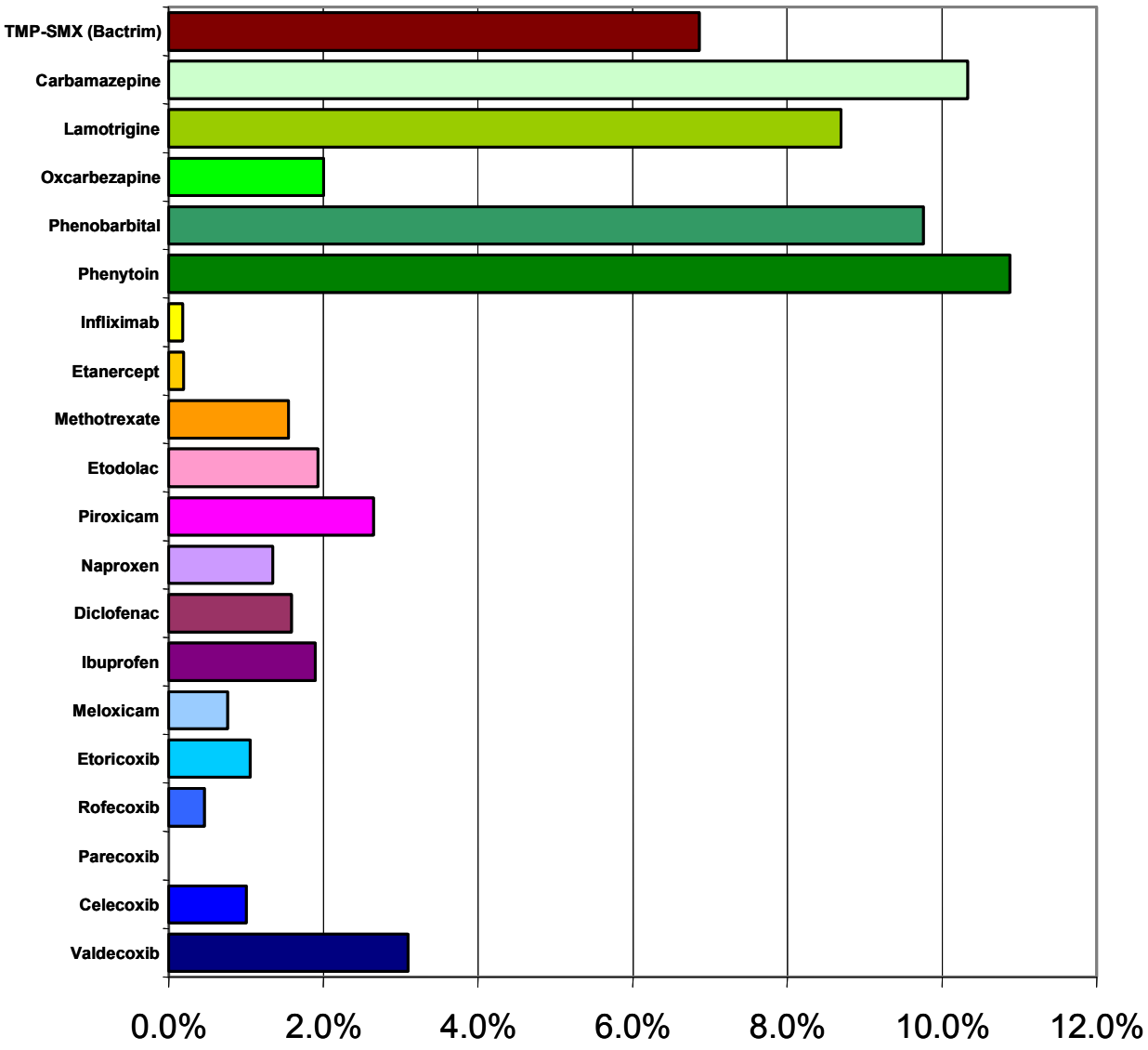
observational studies. There have been no fatalities due to serious skin-related adverse events with either valdecoxib or parecoxib sodium in any clinical study.

4.4. Severe Cutaneous Adverse Reactions (SCAR) With Valdecoxib: Epidemiologic Data

Epidemiologic data are available primarily from the US Food and Drug Administration (FDA) Adverse Events Reporting System (AERS) for US data, and the World Health Organization (WHO) Uppsala Monitoring Center database for ex-US data.

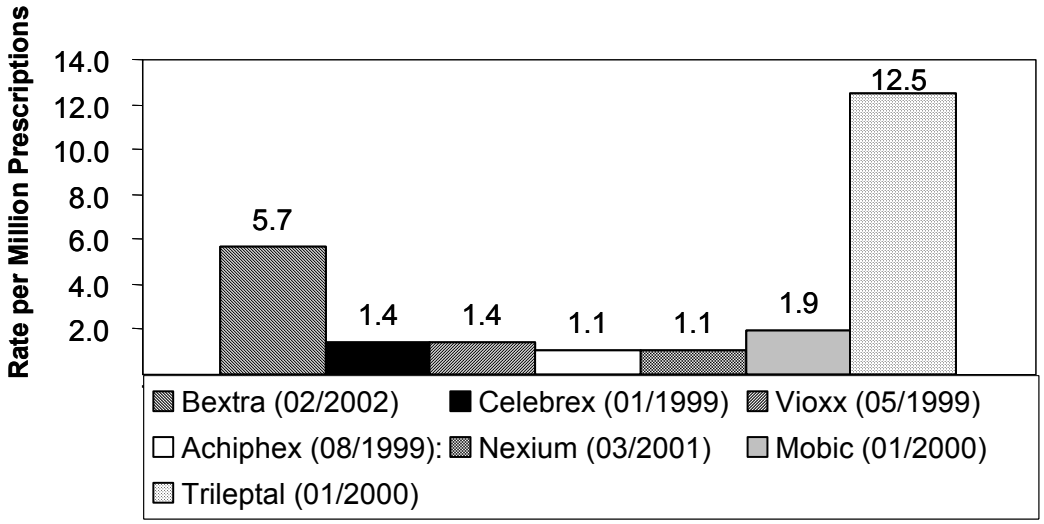
Using WHO data, it is not possible to provide reporting rates based upon the estimate of total person exposure due to a lack of accurate prescription data. As a result, WHO data are reported as total number of SCAR reports per total number of spontaneous adverse reaction reports for the drug. This analysis provides a sense of the relative importance of SCAR to the total side effect profile of a given drug, but does not help assess the absolute incidence of SCAR with particular drugs. As shown in Figure 1, the percentage reporting rate for SCAR with valdecoxib is higher than those observed with other selective COX-2 inhibitors, and is in the same range as many of the NSAIDs such as piroxicam, ibuprofen, and etodolac. Percentage reporting rates for SCAR with valdecoxib appear to be substantially lower than those observed with anti-epileptic agents and with the antibiotic Bactrim (trimethoprim-sulfamethoxazole).

Figure 1. Severe Cutaneous Adverse Reaction (SCAR) Cases as a Percentage of Total Adverse Reaction Reports: World Health Organization (WHO) Data, Ex-US



AERS data, while restricted to the US, can be used to provide reporting rates per million prescriptions, and cumulative rates of SCAR since launch can be calculated for newer products, subject to the limitations of spontaneous reporting rates plus the inherent difficulty in translating numbers of prescriptions into numbers of unique users or unique courses of therapy. Data for several recently launched drugs are displayed in Figure 2. These AERS results, like those above for WHO data, show that the SCAR reporting rate for valdecoxib (Bextra) is approximately four-fold that of celecoxib or rofecoxib, but is well below that observed with the anti-epileptic agent oxcarbazepine (Trileptal).

Figure 2. Adverse Event Reporting System (AERS, US Food and Drug Administration) Cumulative Reporting Rates per Million Prescriptions: Severe Cutaneous Adverse Reactions (SCAR)

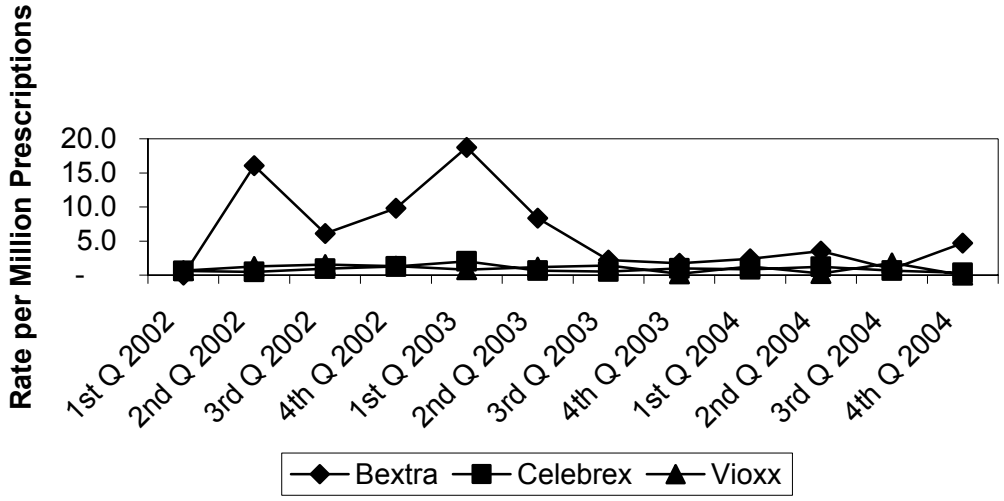


Bextra = valdecoxib; Celebrex = celecoxib; Vioxx = rofecoxib; Achiphex = rabeprazole; Nexium = esomeprazole; Mobic = meloxicam; Trileptal = oxcarbazepine. Data presented are for cumulative rates of SCAR since launch; parentheses indicate launch dates.

A reporting rate for spontaneous adverse events is not a direct measure of risk, as it involves a number of limitations and considerations that should be taken into account with respect to the following: under- or over-estimation of the extent of exposure; under-reporting of actual events; bias in reporting (eg notoriety) and misclassification of reported events. With a 50% error rate in either the exposure estimation or the actual number of cases, estimated SCAR reporting rates for valdecoxib would range from 2.8 (halving) to 11.2 (doubling) events per million prescriptions, approximately 2-fold to 8-fold in excess of the observed rates for either celecoxib or rofecoxib. Nonetheless, even at the high range of SCAR reporting rates, valdecoxib would not be markedly dissimilar from some nonselective NSAIDs as described below. A similar sensitivity assessment with celecoxib would place the reporting rates between 0.7 and 2.8 events/million prescriptions and would not raise any concern relative to any other selective COX-2 inhibitor or nonselective NSAID.

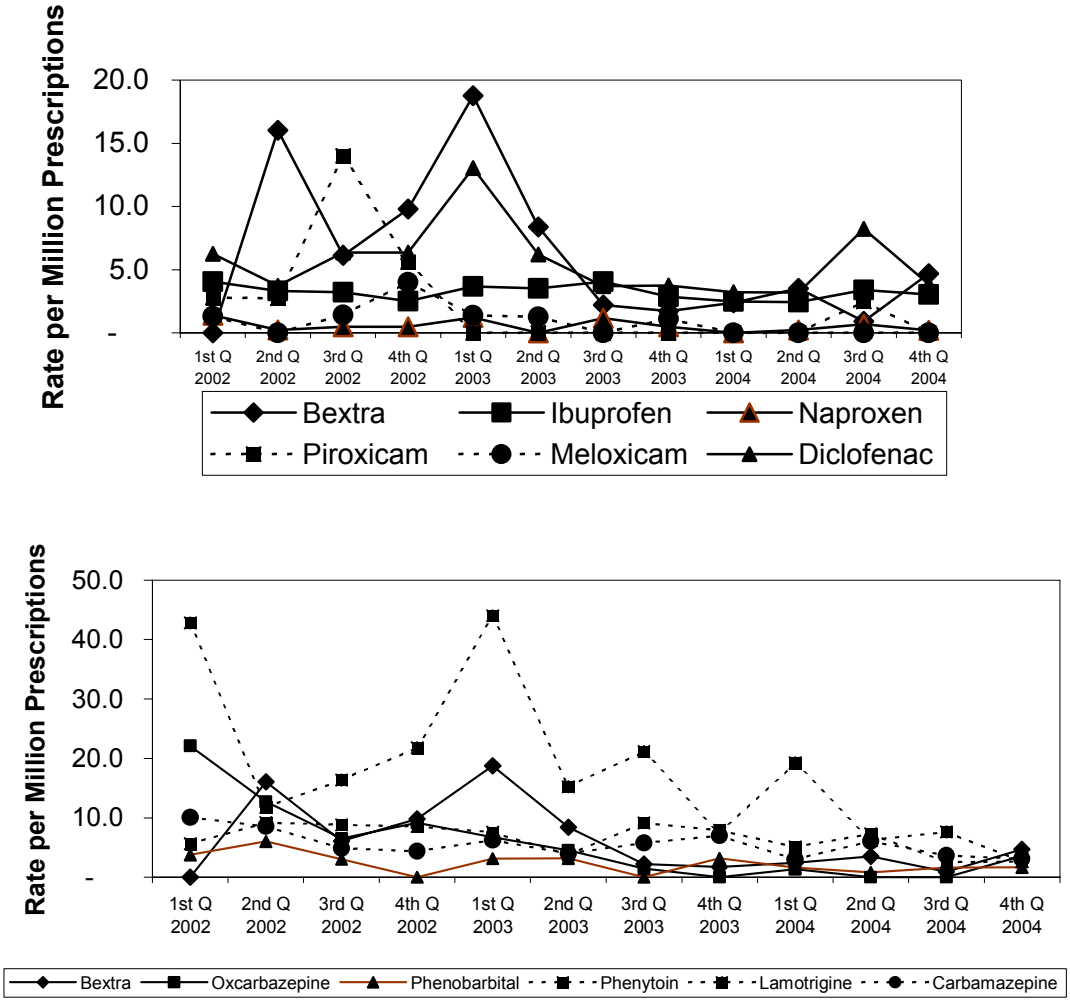
As shown in Figure 3, reporting rates analyzed by quarter for SCAR with celecoxib are comparable to those with rofecoxib. Reporting rates for SCAR with valdecoxib vary from quarter to quarter, peaking immediately after launch and after a communication effort and re-labeling for SCAR in the US during 4Q2002. SCAR reporting rates peaked again after 4Q2004, with institution of a black box warning for SCAR in the US and a widespread communication effort. Although rising as much as 9-fold above the celecoxib and rofecoxib SCAR reporting rates during peaks, the reporting rate of SCAR with valdecoxib during troughs is at about 3-4 fold those of celecoxib and rofecoxib.

Figure 3. Adverse Event Reporting System (AERS, US Food and Drug Administration) Severe Cutaneous Adverse Reactions (SCAR) Reporting Rates per Million Prescriptions: Selective COX-2 Inhibitors



As is evident in Figure 4, quarterly reporting rates for SCAR observed with valdecoxib, even during peak reporting periods, are consistent with the findings in Figure 1 and Figure 2 for overall cumulative rates, ie, they form the upper bounds of the spectrum representing reporting rates with NSAIDs but are not greatly elevated relative to piroxicam or diclofenac during their respective reporting peaks. It should be noted, however, that naproxen and ibuprofen rates may be elevated in this analysis since over the counter (nonprescription) use is not captured in the denominator (number of prescriptions) but may be captured in the numerator (number of events). During peak reporting periods, reporting rates for SCAR observed with valdecoxib are in the range observed for anti-epileptic agents.

Figure 4. Adverse Event Reporting System (AERS, US Food and Drug Administration) Severe Cutaneous Adverse Reactions (SCAR) Reporting Rates per Million Prescriptions: Bextra (Valdecoxib) Versus NSAIDs (Upper Panel) and Bextra Versus Anti-Epileptic Agents (Lower Panel)



4.5. Severe Cutaneous Adverse Reactions (SCAR) With Valdecoxib: Spontaneous Reports

This section reviews data from spontaneous reports of SCAR contained in Pfizer's safety surveillance database for patients reported to have taken valdecoxib. For historical reasons having to do with previous reporting commitments to various regulatory agencies, SCAR cases are presented together with cases of exfoliative dermatitis in summary tables that appear in this section. Spontaneous reports received for valdecoxib to date (cutoff 15 March 2005) are summarized in Table 20.

Table 20. Spontaneously Reported Severe Cutaneous Adverse Reaction (SCAR) Cases With Valdecoxib

Event	Numbers of Cases Reported	
	All Reports	Reports by Healthcare Professionals
SCAR (EM, SJS, or TEN)	186*	160*
Exfoliative Dermatitis	48*	35*
SCAR + Exfoliative Dermatitis	227	188
SCAR Deaths	10	7

SCAR = Severe cutaneous adverse reaction; EM = erythema multiforme; SJS = Stevens-Johnson syndrome; TEN = Toxic epidermal necrolysis.
* A total of 7 cases included exfoliative dermatitis together with EM, SJS, or TEN.

Table 21 shows the spontaneous SCAR reporting rate for valdecoxib in terms of numbers of health care professional-reported cases of SCAR plus exfoliative dermatitis per million patients exposed (estimated from sales data), for each year after launch. The reporting rates shown for valdecoxib are roughly 2 to 3-fold greater than those observed for celecoxib with the exception of the first year of valdecoxib sales, which had a reporting rate 6.4-fold that of celecoxib. This difference may be due to the high number of US SCAR cases reported prior to and immediately following the institution of a sulfonamide allergy contra-indication for valdecoxib in the US.

Table 21. Annual and Cumulative Report Rates for Severe Cutaneous Adverse Reactions (SCAR) With Valdecoxib Reported by Health Care Professionals

	Year Since Launch[a]				Cumulative
	Year 1	Year 2	Year 3	Cumulative	Fatalities
Total SCAR Cases	72	46	70	188	7
Total Patients Exposed[b]	2,453,946	4,736,305	5,580,305	12,952,049	12,952,049
SCAR Cases per Million Patients	29.3	9.7	12.5	14.5	0.5

SCAR = Severe Cutaneous Adverse Reaction; also, for this table, includes exfoliative dermatitis.
[a] Takes into account the fact that valdecoxib was launched in European Union (EU) countries approximately one year later than in non-EU countries; sulfonamide contraindication and skin warnings were included in prescribing information at launch in the EU.
[b] Estimated from sales data provided by IMS and NDC Health.

4.5.1. Severe Cutaneous Adverse Reactions (SCAR) Adjudicated From Spontaneous Reports With Valdecoxib and Parecoxib Sodium

Pfizer in 2002 established a Dermatology Expert Panel (DEP) to review and adjudicate all spontaneous reports of possible SCAR cases on a periodic basis. Among other objectives, the DEP, comprised of Prof. Maja Mockenhaupt, Germany; Prof. Jean-Claude Roujeau, France; and Prof. Robert Stern, USA, was formed to (1) select the skin reactions that would fit the definitions of SCARs and select MedDRA codes to flag for periodic review of cases in the safety surveillance database, and (2) review and adjudicate spontaneous reports of SCAR received by Pfizer for valdecoxib, parecoxib sodium, and celecoxib. From their first review meeting in 2002, the main focus of the DEP has been on diagnosis adjudication (ie, the assessment of the

likeliness of reported diagnoses and, in case a diagnosis was assessed as unlikely, the establishment of a more likely alternative diagnosis), rather than on assessment of case outcomes. Using reports received by Pfizer during the period from 01 July 2001 through 12 March 2005, the DEP has reviewed a total of 221 reports of skin reactions as follows (reports received prior to 01 July 2001 have not been reviewed):

- **Valdecoxib:** A total of 161 reports of SCAR associated with valdecoxib have been reviewed, including 33 reports of EM, 116 reports of SJS, and 12 reports of TEN. The SCAR diagnoses in 29 of these 161 reports (18%) were adjudicated by the DEP as "possible" or "probable." Fatal valdecoxib cases adjudicated as possible or probable include 4 SJS cases and 5 TEN cases. Of these 9 adjudicated fatalities, 8 were reported in elderly patients who were often polymedicated. At the time of this response, one additional valdecoxib case reporting a possible SCAR-related fatality has been received by Pfizer but has not yet been adjudicated; the DEP will review and adjudicate this case at its next meeting.

- **Parecoxib sodium:** A total of 2 reports of skin reactions with parecoxib sodium have been reviewed, one reported as EM (Thailand), and the other reported as exfoliative dermatitis (Greece). The DEP adjudicated both of these diagnoses as "unlikely;" in both cases, urticaria was mentioned as the probable diagnosis. No reports of skin reactions with parecoxib sodium have been adjudicated by the DEP as possible or probable SCAR events.

Reporting rates for SCAR cases adjudicated by the DEP as possible or probable are presented by geographic region in Table 22. These reporting rates are based on cumulative exposure to valdecoxib (ie, number of unique patients exposed) during the period from 01 January 2001 through 28 February 2005, an approximation of the actual exposure time during which cases reviewed by the DEP were reported (ie, 01 July 2001 through 12 March 2005). Overall, reporting rates for SCAR cases with valdecoxib that were adjudicated as possible or probable remain low, ranging from 1.4 to 2.9 cases per million patients, depending on geographic region. Reporting rates for SCAR cases with celecoxib that were adjudicated as possible or probable are lower, ranging from 0.2 to 1.4 cases per million patients. Worldwide, reporting rates for SCAR cases with valdecoxib that were adjudicated as possible or probable are approximately 3 times those with celecoxib; this figure is consistent with figures obtained from both internal and external analyses of non-adjudicated SCAR reports. These rates are also well within the range of SCAR reporting rates for the general population (1-7 events per million patients), despite differences in methodology.

Table 22. Reporting Rates for Cases of Severe Cutaneous Adverse Reaction With Valdecoxib, Adjudicated as Possible or Probable

	USA	Europe[a]	Ex-US, Ex-Europe[b]	Worldwide
N	8,723,512	842,652	704,891	10,971,055
SCAR Cases	26	2	1	29
Rate	2.9	2.3	1.4	2.9

N = Number of unique patients exposed from 01 January 2001 through 28 February 2005;
SCAR Cases = Spontaneously reported cases adjudicated as possibly or probably severe cutaneous adverse reactions by a Dermatology Expert Panel; Rate = Number of SCAR cases per million patients.

[a] Includes: Austria, Belgium, Czech, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Netherlands, Norway, Poland, Portugal, Slovakia, Spain, Sweden, Switzerland, United Kingdom. As of 31Dec04, valdecoxib was available in all of these countries except Denmark, Estonia, France, Hungary, Latvia, Lithuania, Poland, Portugal, Spain; valdecoxib was not launched in most EU countries until 2004.

[b] Includes: Argentina, Australia, Brazil, Central America, Canada, Chile, China, Columbia, Dominican Republic, Ecuador, Egypt, French West Africa, Hong Kong, Indonesia, Israel, Jordan, Korea, Kuwait, Latvia, Lebanon, Lithuania, Luxembourg, Malaysia, Mexico, Morocco, New Zealand, Pakistan, Peru, Philippines, South Africa, Saudi Arabia, Singapore, Taiwan, Thailand, Tunisia, Turkey, United Arab Emirates, Venezuela.

4.5.2. Severe Cutaneous Adverse Reactions (SCAR) With Valdecoxib: Demographics and Predisposing Factors in Spontaneous Reports

Through 15 March 2005, healthcare professionals have reported a total of 188 cases of SCAR with valdecoxib. This total includes 35 reports of exfoliative dermatitis. Of these 188 cases, the duration of therapy at the event onset is known for 68 (36%) of the events. In 60 of these 68 events (88%), the onset was reportedly less than one month after initiation of therapy, and in 44 of the 68 events (64%), the onset was within one week of the initiation of therapy. Total daily valdecoxib doses were reported for 115 of these 188 cases. In 34/115 (30%) of the cases reporting dose information, the daily dose was 10 mg or less; in the remaining cases (70%) the daily dose was greater than 10 mg. Consistent with the demographic profile of patients with OA or RA and the approved indications for valdecoxib, the majority of SCAR events occurred in patients greater than 50 years of age. Among cases reporting concomitant medications, patients were receiving concomitant drug therapy with other agents known to be associated with risk of SCAR (eg, carbamazepine, lamotrigine, phenytoin) in 21 cases (11%). Approximately 11% of reported SCAR cases were in patients with a history of sulfonamide allergy, and another 13% of reported SCAR cases were in patients who had previously experienced some other form of drug allergy.

In summary, the results of analysis of spontaneous reports of SCAR with valdecoxib are consistent with the medical literature and provide a rationale for the risk management plan specifically proposed for valdecoxib. In particular, dose minimization, close physician observation of the patient following initiation of therapy, and exclusion of patients with presumed susceptibility due to medical history or concomitant drug therapy would appear to be appropriate evidence-based strategies for reducing the risk of SCAR with valdecoxib.

5. BENEFIT/RISK ASSESSMENT

An estimated 4 million Canadians are suffering from arthritis and other rheumatic conditions. In 1998, arthritis and related conditions were the underlying cause of 2.4 deaths per 100,000 in Canada, making arthritis a more common underlying cause of death than melanoma, asthma, or HIV/AIDS; overall, approximately 12% of Canadians aged 65 years or older were prescribed nonselective NSAIDs in the year 2000, most for the treatment of arthritis and other rheumatic conditions.[44] The nonselective NSAIDs have been widely used for decades despite their risks because they serve a significant medical need and allow mobility and relief from chronic pain. Due to this widespread use, concern regarding the risk of gastrointestinal adverse effects with nonselective NSAIDs, together with new concerns regarding possible cardiovascular safety signals recently observed in preliminary data from the APPROVe and APC trials, will complicate benefit/risk considerations for all NSAIDs, both nonselective and selective COX-2 inhibitors.

Approximately 3.6 times as many NSAID prescriptions are written for elderly patients compared to younger patients.[45] Eighty percent of adults >65 years of age have radiographic evidence of OA, virtually all have this disease by the age of 80,[46] and half of all NSAID prescriptions in the elderly are for this indication.[47] Changes in the usage patterns for selective COX-2 inhibitors and nonselective NSAIDs will affect large numbers of patients in Canada and worldwide, and the problem will increase in scope as populations increase in average age. Increased use of nonselective NSAIDs in an aging population will increase the numbers of gastrointestinal, cardiorenal, and possibly cardiovascular adverse events related to NSAID use. It has been estimated that 5% to 7% of US hospital admissions are related to adverse effects associated with medication use, and hospitalizations for gastrointestinal, nervous system, renal, or allergic effects associated with use of aspirin or non-aspirin nonselective NSAIDs are responsible for approximately 30 percent of this total.[48] In OA patients the balance of positive effects measured against the potential adverse effects is particularly critical given the increased potential for NSAID-induced toxic effects mediated partially by age.

5.1. Valdecoxib Treats Osteoarthritis and Rheumatoid Arthritis Effectively

In randomized, controlled clinical trials, valdecoxib 10-20 mg QD has consistently demonstrated significant improvement in OA patients compared to placebo using standard measures for clinical responses (American Pain Society Pain Measurement Scale; Western Ontario and MacMaster Universities Osteoarthritis Index [WOMAC], an assessment of pain, stiffness, and functional outcome). The degree of efficacy observed with valdecoxib was comparable to that observed with the full recommended dose of naproxen for the treatment of OA, with symptomatic relief generally evident at the first clinically measured interval and maintained for up to 48 weeks of continuous therapy. The beneficial OA treatment response with valdecoxib is predictable and comparable in all patient groups studied, and does not appear to be affected by age, gender, disease duration or severity, or use of concomitant medications. Adjustment of valdecoxib dose due to age, weight, or arthritis disease status is not necessary in order to achieve a maximum response. These results conclusively demonstrate the beneficial effects of valdecoxib in treatment of the signs and symptoms of OA, indicating that it is a predictably

efficacious, easily managed treatment that provides efficacy similar to that observed with other widely used and effective NSAID therapies.

Randomized, controlled clinical trials have also shown that valdecoxib 10-20 mg QD is effective for the treatment of the signs and symptoms of RA. Placebo and nonselective NSAID-controlled trials of 6 to 26 weeks duration utilizing several using standard measures for clinical responses (American College of Rheumatology 20% Responder Index, Patient's Assessment of Arthritic Pain--Visual Analog Scale, health-related quality of life as measured by the disease-specific Modified Health Assessment Questionnaire) consistently demonstrated significant anti-inflammatory and analgesic efficacy compared to placebo that was generally comparable to the efficacy of nonselective NSAIDs. When compared to naproxen 500 mg BID, patients who received valdecoxib 20 mg QD had a somewhat better response than patients who received 10 mg QD. Additionally, in a recently completed double-blind, randomized, placebo-controlled, 12-week study (Study A3471018), valdecoxib 10 mg QD was had comparable efficacy compared to naproxen 500 mg QD in treating the signs and symptoms of RA in a patient population with RA in a severe flare state. Efficacy was observed with valdecoxib 10 mg QD from the first clinic visit (Week 1) through the end of the study. Patient responses to valdecoxib in RA were consistent across studies and were not affected by age, gender, disease severity or duration, or use of concomitant medications including corticosteroids, methotrexate or disease modifying anti-rheumatic drugs; thus, no special considerations or dose adjustments are required with these medications. Further, a sustained beneficial response has been demonstrated for periods up to 12 months. Thus, valdecoxib RA trials provide a conclusive demonstration that valdecoxib provides meaningful anti-arthritic benefit to patients with RA comparable to that provided by a widely-used nonselective NSAID.

A controversial question in the management of OA is whether NSAIDs are superior to simple analgesics with respect to pain relief. Nonselective NSAIDs have been shown to provide benefits including reduced pain, decreased gel phenomena, and improved function in OA patients;[49] it is not clear whether any of these benefits are due specifically to anti-inflammatory effects. Recently, 3 important trials have revisited the question of the importance of NSAIDs in the treatment of patients >40 years of age with OA of the hip or knee. These double-blinded, randomized, controlled trials used a crossover design to compare the effects of NSAIDs versus acetaminophen in OA. The crossover design allowed patients to assess and compare treatments: Patients were treated for six weeks in each of 2 treatment periods, with a washout period separating the 2 treatment periods; active treatments were diclofenac/misoprostol, (a nonselective NSAID and gastroprotectant in fixed combination) 75 mg/200 mcg BID versus acetaminophen 1000 mg QID in one trial,[50] and celecoxib 200 mg/day versus acetaminophen 4000 mg/day in the other 2 trials.[51] In the respective trials, both diclofenac/misoprostol and celecoxib were always numerically and usually statistically superior to acetaminophen in a patient assessment of pain using visual analog scale and in the WOMAC. Adverse events were significantly more common with diclofenac/misoprostol treatment than with acetaminophen, but the safety profile of celecoxib was indistinguishable compared to that of acetaminophen. Patient preferences significantly favored both diclofenac/misoprostol and celecoxib over acetaminophen. Together, these data suggest that in patients whose pain is associated with a low-grade inflammatory process, medications with both anti-inflammatory and analgesic activities provide superior efficacy compared to a simple analgesic.

5.2. Valdecoxib Offers a Gastrointestinal Benefit

The incidence rates for serious gastrointestinal complications among non-users of NSAIDs are 0.9 events per 1000 person-years (95% CI: 0.66 to 1.27) for bleeding or perforated lesions, and 1.0 events per 1000 person-years (95% CI: 0.83 to 1.15) for serious gastrointestinal ulcer; rates increase with age, and are approximately twice as high in men compared to women.[52] In a systematic review of epidemiology studies conducted from 1990 to 1999, the risk of upper gastrointestinal bleeding was four times greater in nonselective NSAID users relative to non-users of NSAIDs (pooled relative risk 3.8; 95% CI: 3.6 to 4.1).[53] Because COX-1 acts constitutively in the gastric mucosa to produce prostaglandins that promote generation of a protective mucous barrier lining the gastric lumen,[54-56] the most clinically significant and well-characterized adverse effects with nonselective NSAIDs are related to the degradation of this protective barrier. As a result, such agents may precipitate a variety of pathologies including esophagitis, esophageal stricture, gastritis, mucosal erosions, hemorrhage, the development of peptic ulcer or its complications including perforation and obstruction.[57-61] Additionally, there is increasing evidence of small and large bowel mucosal effects including induction of both gut permeability dysfunction and strictures with resulting obstruction.[62-64]

It has been demonstrated in endoscopic studies that nonselective NSAIDs classically produce shallow erosions or submucosal hemorrhages which can occur at any site in the alimentary tract but more commonly are observed in the stomach near the prepyloric area and the antrum. Typically, many of these gastrointestinal lesions are asymptomatic, making prevalence data very difficult to determine. Unfortunately, we also do not know what proportion of these lesions typically progress to develop ulceration and then extend to frank perforation, obstruction of the viscous, or serious gastrointestinal hemorrhage and subsequent death. Although many patients develop important gastrointestinal damage with no warning, there are known risk factors for the development of gastrointestinal effects with nonselective NSAIDs. These risk factors include increased age; history of peptic ulcer disease or gastrointestinal bleeding; prior use of antiulcer therapy for any reason; concomitant use of glucocorticoids, particularly in patients with rheumatoid arthritis; comorbid illness such as significant cardiovascular disease; and extensive or severe rheumatoid arthritis.[65-68] Additionally, combinations of NSAIDs can increase the risk for significant gastrointestinal adverse effects, and all of the presently available nonselective NSAIDs when used at high enough anti-inflammatory doses may induce significant damage to the gastrointestinal mucosa.

Thus, the nonselective NSAIDs are clearly associated with increased risk for clinically important gastrointestinal events that may lead to increased risk of death directly related to therapy. The COX-1 sparing effects of valdecoxib are associated with evidence of less mucosal damage as demonstrated in clinical trials. Representative results are as follows:

- In a surveillance endoscopy trial in which 1052 OA patients were randomly assigned to valdecoxib 10 or 20 mg QD, ibuprofen 800 mg TID, diclofenac 75 mg BID or placebo for 12 weeks.[69] All doses of valdecoxib, ibuprofen, and diclofenac improved signs and symptoms of arthritis compared to placebo. The incidence of endoscopically determined gastroduodenal ulcers among patients taking valdecoxib (10 mg QD: 5%, 20 mg QD: 4%) was similar to that observed with placebo (7%) and was significantly lower than observed with ibuprofen 800 mg TID (16%) and diclofenac 75 mg BID (17%).

- In a 26-week study comparing supratherapeutic doses of valdecoxib (20 to 40 mg QD) versus diclofenac 75 mg SR BID in RA patients, both doses of valdecoxib were comparable in efficacy to diclofenac while demonstrating significantly lower rates of endoscopically determined gastroduodenal ulcers (valdecoxib 20 mg QD: 6%, 40 mg QD: 4%, and diclofenac 75 mg BID 16%; $p < 0.001$).[70]

- In a recently published pooled analysis from 8 double-blind, randomized, controlled trials and three long-term, open-label trials, the rate of upper gastrointestinal ulcer complications with valdecoxib was compared to nonselective NSAIDs.[71] This analysis, which was prespecified, included 7434 OA and RA patients who received double-blind placebo (n = 973), valdecoxib 5-80 mg daily (n = 4362), or a nonselective comparator NSAID (naproxen, ibuprofen or diclofenac; n = 2099) for 12-26 weeks. All potential upper GI events were reviewed and adjudicated by a blinded, independent review committee based on prespecified definitions of ulcer complications (perforations, obstructions, bleeds). Valdecoxib 10-80 mg daily was associated with a significantly lower rate of upper gastrointestinal ulcer complications compared to nonselective NSAIDs both in the all patients cohort (0.68% versus 1.96%, respectively; $p<0.05$) and among nonusers of aspirin (0.29% versus 2.08%, respectively; $p<0.05$).

- Pooled analysis from 2871 additional patients with OA or RA who were treated with valdecoxib 10-80 mg daily for periods up to one year in open label safety trials are consistent with data from valdecoxib-treated patients in the pooled analysis of controlled trials described above.[71] Thus, increasing length of exposure to valdecoxib does not confer added risk for the development of ulcer complications. In these long-term, open label trials, the annualized incidence of clinically significant upper gastrointestinal with valdecoxib in the all patients cohort was 0.39%; among nonusers of aspirin the annualized incidence was 0.2%.

Regarding gastrointestinal tolerability, a meta-analysis was recently published that included data from five double-blind, randomized, placebo-controlled, 12-week trials representing 4394 OA and RA patients who received placebo (973 patients) valdecoxib 10 mg daily (955 patients), valdecoxib 20 mg daily (851 patients), valdecoxib 40 mg daily (430 patients) or a nonselective comparator NSAID: naproxen 1000 mg daily (766 patients), ibuprofen 2400 mg daily (207 patients) or diclofenac 150 mg daily (212 patients).[72] In this meta-analysis, valdecoxib 10-40 mg daily was associated with significantly fewer reports of moderate-to-severe upper gastrointestinal adverse events (abdominal pain, dyspepsia, and nausea) than were combined nonselective NSAIDs (hazards ratio = 0.59; 95% CI: 0.47 to 0.74, $p < 0.001$); valdecoxib was comparable to placebo in terms of overall upper gastrointestinal adverse events. Moreover, in time-to-event analyses, improved tolerability with valdecoxib relative to combined nonselective NSAIDs for moderate-to-severe upper gastrointestinal adverse events was apparent as early as the first week of treatment and was maintained throughout the 12-week treatment period. Thus, valdecoxib was well tolerated in comparison to nonselective NSAIDs.

In summary, data from clinical trials with chronic administration in OA and RA patients has shown significant advantages with valdecoxib over nonselective NSAID comparators with regard to gastroduodenal ulcers, clinically significant upper gastrointestinal events, and gastrointestinal tolerability, representing an important, medically significant benefit.

5.3. Valdecoxib Cardiovascular Safety

The possibility of increased cardiovascular risk with rofecoxib was first evident in clinical trials data with the results of the VIGOR trial, in which 8076 patients with OA or RA were treated for a median duration of 8 months with rofecoxib or naproxen.[73] The recent preliminary observation of increased cardiovascular risk with rofecoxib compared to placebo in the APPROVe trial is consistent with the VIGOR result, and shows increased risk with increasing rofecoxib dose.[74] In contrast, no statistically significant increase in cardiovascular safety risk was observed with valdecoxib relative to either placebo or nonselective NSAIDs either in individual studies with OA and RA patients or in a meta-analysis of 19 randomized, controlled trials representing 7061 patients treated with valdecoxib doses ranging from 1 to 80 mg TDD for durations of 2 weeks up to 1 year (most patients were treated with valdecoxib in studies with up to 3 months duration); however, due to small numbers of events, confidence intervals were very wide for comparisons between valdecoxib and either placebo or nonselective NSAIDs (Section 2.2). There have been no valdecoxib clinical trials longer than 1 year in duration, and no epidemiology studies have been published that evaluate cardiovascular thromboembolic adverse events in patients taking valdecoxib.

The only cardiovascular safety signal observed with valdecoxib has been the apparent increase in cardiovascular risk in CABG Surgery Studies 93-035 and 93-071, in which serious cardiovascular thromboembolic events were among a set of clinically relevant adverse events prespecified for adjudication (Section 2.3). No cardiovascular safety signal was observed in Study 93-069 (Section 2.3.3), in which 525 patients treated with parecoxib sodium/valdecoxib 40 mg TDD were compared to 525 patients treated with placebo/placebo for 10 days post-surgery (3 days intravenous treatment followed by 7 days oral treatment), a design virtually identical to the design of CABG Surgery Study 93-071. Likewise, in a post hoc analysis of data from 17 non-cardiac surgery/ankle sprain studies, evaluated for adverse event terms matching those adjudicated as clinically relevant adverse events in Studies 93-069 and 93-071, no increase was observed with valdecoxib 20-60 mg TDD (3076 patients) compared to placebo (1965 patients) in adverse events or serious adverse events in the cardiovascular or renal categories. In 2 subsequent post hoc analyses of integrated data from acute pain studies excluding CABG Surgery Studies 93-035 and 93-071 (data not shown), there were no significant differences in cardiovascular events comparing valdecoxib (all doses combined, ie, 20-80 mg TDD; 2319 patients) versus placebo (1311 patients) using data from all 15 randomized, controlled, valdecoxib-only (ie, no intravenous parecoxib sodium treatment preceding oral valdecoxib treatment) surgery/ankle sprain trials to date or comparing parecoxib sodium/valdecoxib (all doses combined, ie, 20-80 mg TDD; 5285 patients) versus placebo (3226 patients) using data from all 32 randomized, controlled trails to date in which patients were treated with parecoxib sodium, valdecoxib, or both.

The results from randomized, controlled trials described above clearly demonstrate that the cardiovascular safety risk apparent with parecoxib sodium/valdecoxib in CABG Surgery Studies 93-035 and 93-071 is not present in patients taking parecoxib sodium, valdecoxib, or both in the setting of general surgery nor in patients with OA or RA taking valdecoxib daily for up to 1 year (most patients were treated with valdecoxib in studies with up to 3 months duration). Currently, there are no published data regarding the effect of treatment with nonselective NSAIDs or selective COX-2 inhibitors other than parecoxib sodium/valdecoxib on cardiovascular risk in

post-CABG surgery patients, and hence no way to put the cardiovascular safety risk apparent with parecoxib sodium/valdecoxib in CABG Surgery Studies 93-035 and 93-071 into clinical context.

The important question is whether the cardiovascular safety signal apparent with parecoxib sodium/valdecoxib in CABG Surgery Studies 93-035 and 93-071 amounts to a warning that increased cardiovascular risk can reasonably be expected with long-term valdecoxib treatment (eg, in large, long-term OA/RA studies like VIGOR or in the larger, longer-term APPROVe cancer prevention study). In this regard, it should be noted that CABG surgery patients are normally considered to be at high risk for postoperative adverse events due to risks inherent in anesthesia, cardiac surgery, cardiopulmonary bypass procedures, and underlying cardiovascular disease. In particular, cardiopulmonary bypass procedures are often associated with a systemic inflammatory response syndrome that can be induced by at least 3 mechanisms:[16] exposure of blood to the plastic tubing and oxygenation systems used to maintain extracorporeal circulation; ischemic reperfusion injury to brain, heart, lungs, kidney, and liver caused by periods of aortic cross-clamping; and splanchnic ischemia that may result in the systemic release of endotoxin. In this setting, COX-2 is up-regulated, and TxA_2 appears to be elevated by multiple mechanisms including heparin-protamine interaction;[17] this increase in TxA_2 may be severe enough to cause pulmonary hypertension. Also, cardiopulmonary bypass procedures activate and partially deplete circulating platelets, and platelet regeneration following surgery is markedly increased, resulting in an apparent "aspirin resistance" if aspirin is administered QD only (ie, because the plasma half-life of aspirin is very short, QD administration is insufficient to produce circadian platelet inhibition when new platelets are generated at a rate higher than normal). Interactions between the various pro- and anti-thrombotic and -inflammatory mediators that contribute to these effects and their clinical consequences are not well understood.[16]

In summary, the first few days after cardiopulmonary bypass procedures represent a unique and highly dynamic pro-thrombotic and inflammatory syndrome, with effects on cardiovascular morbidity that are orders of magnitude greater than those seen in other types of surgery,[18] giving rise to complication rates of 15% or higher that affect the heart, brain, kidneys, or intestinal function.[19] Nearly 13% of CABG surgery patients discharged following the procedure are readmitted to the hospital within 30 days due to complications of the surgery, including infection, congestive heart failure, myocardial infarction/ischemia, and arrhythmias.[20] These observations, together with the data from general surgery/ankle sprain studies and OA/RA studies described above, suggest that safety concerns identified in the CABG surgery patient population may be limited to that population and cannot be generalized to the broader general surgery patient population.

5.4. Severe Cutaneous Adverse Reactions (SCAR) Observed With Valdecoxib

Safety analysis of serious skin reactions based on data from clinical studies, epidemiology studies, and spontaneous reports (Section 4) supports the conclusion that the reporting rate of SCAR with valdecoxib is several-fold higher than that observed with other selective COX-2 inhibitors, is only marginally worse than the rates observed with some nonselective NSAIDs, and is generally lower than rates observed with anti-epileptic agents. In response to this observation, and to build on previous risk management efforts, Pfizer is proposing a series of risk management actions to enable the resumption of availability of valdecoxib to OA and RA

patients in Canada. Collectively it is estimated that these actions would reduce the risk of fatal SCAR reactions several-fold, bringing the rates of SCAR-related fatalities and irreversible sequelae more in line with those of other anti-inflammatory agents.

- Pfizer proposes to amend prescribing information to limit the indicated use of valdecoxib in OA and RA to patients who have failed to respond to or could not tolerate nonselective NSAIDs and other selective COX-2 inhibitors. This would reduce total valdecoxib use (and assure use is in a setting where a specific benefit offsets the risk) and hence would reduce the total number of SCAR cases.

- Because dosage is a risk factor for SCAR, and because the risk may be similar or increased with each recurrent use, Pfizer proposes to remove the indication for valdecoxib in primary dysmenorrhea. This indication requires the highest daily dose and typically calls for intermittent use of valdecoxib that could possibly expose the user to repeated cycles of high initial therapy risk.

- Because 90% of the documented cases with valdecoxib occur within the first 3 weeks of therapy, epidemiology studies show a marked decrease in risk after several weeks of therapy; and prompt withdrawal of the offending agent is the most effective treatment for SCAR, it is proposed that there be more frequent and intense monitoring of patients taking valdecoxib during this initial period. In addition, prescribing information and patient and physician education materials will stress the importance of immediate discontinuation of valdecoxib and notification to the treating physician at the first evidence of dermal and/or mucosal signs or symptoms, especially during the first month of therapy. Pfizer will work with regulatory agencies in Canada and elsewhere to develop programs to assure compliance with these measures.

5.5. Benefit/Risk Conclusions

For patients with the chronic inflammatory pain of OA and RA, there are few therapeutic alternatives. Opioids are not effective against inflammatory conditions and are addictive, and acetaminophen efficacy is inadequate for many patients. The only remaining options are NSAIDs, whether nonselective or selective COX-2 inhibitors. As a result, patients requiring both anti-inflammatory and analgesic relief who discontinue treatment with selective COX-2 inhibitors will turn to nonselective NSAIDs. This treatment alternative may actually increase overall risk, as the gastrointestinal safety of the nonselective NSAIDs is inferior and the cardiovascular risk may be similar to that with selective COX-2 inhibitors.

Weighing the available total evidence, it appears that, as with the nonselective NSAIDs, all selective COX-2 agents are not alike. Furthermore, there is clear evidence that there are some patients who derive significant benefits using selective COX-2 inhibitors. These medications are equally efficacious compared to nonselective NSAIDs in multiple chronic and acute situations. In addition, for certain patients the selective COX-2 inhibitors provide a better gastrointestinal safety profile than nonselective NSAIDs. These patients are typically older and require chronic pain relief, but are at higher baseline risk for gastrointestinal adverse events and associated complications. It is also clear that these patients may have increased baseline risk for cardiovascular thromboembolic events. Only further study will allow an understanding of

apparent cardiovascular risks weighed against the known risks for gastrointestinal complications associated with nonselective NSAIDs and selective COX-2 inhibitors, and whether all of the selective COX-2 inhibitors carry the same risk.

Safety analysis of serious skin reactions based on data from clinical studies, epidemiological studies, and spontaneous reports, which are consistent with the medical literature, supports the conclusion that the reporting rate of SCAR with valdecoxib, though several-fold higher than that observed with other selective COX-2 inhibitors, is only marginally worse than the rates observed with some nonselective NSAIDs, and is generally lower than rates observed with anti-epileptic agents. Hence, the risk of SCAR with valdecoxib is manageable with the measures described above. In light of this manageable risk, together with the cardiovascular and gastrointestinal safety considerations described above and the potential for benefit in patients who cannot tolerate or do not respond to nonselective NSAIDs or other selective COX-2 inhibitors, it is important to continue to allow access to valdecoxib for OA and RA patients.

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