

Agent: Valdecoxib
Indication: Analgesia, Dysmenorrhea Osteoarthritis, and Rheumatoid Arthritis
Reviewer: Kent Johnson, MD
Date: November 7, 2001
NDA: 21,341

EXECUTIVE SUMMARY

1-RECOMMENDATIONS

A. Approval for the indications of osteoarthritis and rheumatoid arthritis at a dose of 10mg/day and dysmenorrhea at a dose of 20-mg bid as needed.

B. Nonapproval of the acute pain, including opioid-sparing and prevention of operative pain. The only substantial multidose safety database is found in the Coronary Artery Bypass Graft (CABG) Surgery study 035. This study demonstrated an excess of serious adverse events including death in association with the use of paracoxib and valdecoxib 40 mg bid when added to ad lib parenteral narcotic analgesia. The allocation was 2:1 drug versus placebo and the population was highly enriched with patients at high risk for cardiovascular thromboembolic events. Therefore, interpretation of these findings cannot be conclusive at this time. These finding warrants further investigation before valdecoxib can be considered safe and effective for the treatment of pain, particularly multidose therapy in the perioperative setting. The dose used in the CABG trial was eightfold higher than the dose proposed for approval for the treatment of osteoarthritis and rheumatoid arthritis and twice the dose proposed for the treatment of dysmenorrhea. In addition the proposed populations is distinctly different than the post-operative setting. The extensive safety database at 10-80mg daily in the arthritis safety database is adequate to support approval of the chronic therapy at 10 mg/day for arthritis and acute dose of 20 mg bid for short term use in dysmenorrhea.

2-SUMMARY OF CLINICAL FINDINGS

a) Adequate efficacy has been demonstrated in osteoarthritis and rheumatoid arthritis at 10mg/d with no additional efficacy at 20mg/d. The safety profile with chronic use in RA and OA is adequate at 10mg/d. At higher total daily doses, the findings of more hypertension and edema are frequently reproduced, and they are formally affirmed in a prospective manner in Trial 47, which directly tested the hypothesis of renal safety at 40 and 80 mg/day. In the analysis of older subpopulations over the age of 65 years edema and hypertension appear to be greater at 20 mg/day compared to 10 mg/ day.

b) Single-dose analgesia has been demonstrated at 20mg and 40mg in the dental, dysmenorrhea, with supportive data from other surgical models.

c) Two studies (024, 037) evaluating prevention or pre-emption of post-operative pain demonstrated the superiority of valdecoxib 20, 40 and 80 mg over placebo for the

endpoints of time to rescue medication as well as proportion of patients taking rescue medication. There was no difference in pain intensity over the first 2 hours in study 024 and 4 hours in study 037. This finding raises concern over the value of preoperative management of post-operative pain, particularly in regards to the risk versus potential benefit.

Data from these two studies should not be considered for labeling until the overall clinical value of such treatment is further defined as well as the safety. Pre-operative dosing should be compared to post-operative dosing to adequately characterize the value of pre-operative treatment given the lack of differentiation in pain intensity between valdecoxib and placebo treated subjects.

d) Three studies of opioid sparing were submitted (Trials 35, 51, and 38). While mean opioid dose was lower in subjects treated with valdecoxib 40mg bid in the three studies, results were not replicated for 20-mg bid. Decreases in peak pain intensity were demonstrated in two of the three studies at 40 mg bid. This finding was not replicated for the 20-mg bid dose. Sparing of adverse events was not demonstrated in these studies. In study 035 there was a statistically significant excess of serious adverse events associated with the use of valdecoxib 40-mg bid when added to ad lib narcotic therapy compared with narcotic analgesia alone. The value of “opioid sparing based on numeric differences in total opioid requirement is of unclear and unproven clinical benefit.

e) No efficacy advantage was demonstrated or suggested for valdecoxib compared to:

- i. ibuprofen, naproxen and acetamenophen/oxycodone in analgesic studies
- ii. naproxen, ibuprofen or diclofenac in osteoarthritis studies
- iii. naproxen in rheumatoid arthritis studies

3-OVERVIEW OF CLINICAL PROGRAM ANALGESIA:

This NDA consists of a program of analgesia trials to support a claim for acute pain, and a number of trials in osteoarthritis and rheumatoid arthritis to support a claim for chronic use in these conditions. The analgesia program tended to follow drug development programs for acute pain used in the past, relying heavily on single-dose demonstrations of efficacy compared to placebo and active controls, plus PK support demonstrating blood level stability over time and a satisfactory chronic risk/benefit from different indications (osteoarthritis and rheumatoid arthritis) to then *extrapolate* the safety for multiple-dose use in acute pain. The following is the sponsor’s request for claims:

An indication for the treatment of acute pain and dysmenorrhea at 40mg/d, with an additional 40mg on day one if needed, and an indication for chronic treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis at a dose of 10mg/day, with the proviso that “some may receive additional benefit at 20mg/day.”

It should be noted that there was the usual interaction with the sponsor regarding the scope and content of their development program. These interactions were more prescriptive in the case of OA and RA, as RA had been recently addressed in a Guidance Document, and the former had been the topic of a number of public meetings during which certain fundamentals such as trial duration, primary endpoints, and statistical

methodology, were established. Thus, there was a priori agreement regarding data assessment in OA and RA, but the same cannot be said of analgesia. The agency, in collaboration with outside bodies, has been and remains in the process of formulating current analgesia guidelines, and, in particular, the nature of the evidence base needed to demonstrate efficacy in analgesia. A weakness in the approach used in the past is the extrapolation needed to assert multiple dose efficacy, rather than having data directly supporting this. In the past, this approach, although not ideal, was deemed acceptable given that agents were drugs which were administered orally and usually showed identical dosing in both the analgesia and arthritis settings. Furthermore, pharmacokinetic parameters would suggest higher rather than lower levels on re-medication in the acute multi-dose setting. In addition, in many to most acute pain settings, pain intensity typically diminishes rather than increase over time (suggesting that analgesia that is documented to be effective at the time of maximum pain would continue to be adequate as time passed).

An area where extrapolation cannot be made is in the assessment of dosing interval. Single dose efficacy data alone is less robust than comparative multi-dose data in assessing the optimal dosing interval. Although the division is exploring approaches which yields direct multiple-dose evidence and so depends less on extrapolation, the interactions for this NDA preceded this, so in this review the single-dose to multiple-dose extrapolation will be accepted. It is of note that supportive evidence of multi-dose efficacy was submitted by the sponsor although studies were not designed to rigorously assess the multi-dose period.

The analgesia program consisted of nineteen trials -- seven dental, two dysmenorrhea, and ten in various surgical settings. Only four were designed as multiple-dose trials. The other fifteen all were explicitly designed as single-dose. These trials could not provide multiple dose evidence of efficacy or dosing interval because: (1) The election of a very early time as the explicit, or de facto (as evidenced e.g. by its use in the powering of the trial) time-point for the primary analysis (ten trials using the 45 min PID for powering), and (2) the absence of re-dosing of short duration, active controls (ibuprofen or oxycodone/acetaminophen).

The dysmenorrhea trials were both 4-part crossover designs. Two surgery trials were designed to test the use of valdecoxib in a pre-emptive manner, given shortly before surgery. All trials were both placebo and active controlled except three which were designed to test a morphine-sparing hypothesis the pre-operative and the two pre-operative dosing studies. The three morphine-sparing trials allowed ad lib morphine use in both arms, so, in effect, they employed a "standard-of-care" as the control arm. The inclusion criteria varied widely across these designs, from patients undergoing the standard third molar extraction in the dental trials, to patients undergoing various modes of anaesthesia delivery (local, regional, spinal, general). This diversity has always been encouraged, as pertinent to any claim is a presumption of generalizability. In this NDA Trial 35 attempted to capture patients with substantial co-morbidity by enrolling patients who had undergone coronary artery bypass graft (CABG) surgery. This was an efficacy

as well as a safety trial. The “COX-2 hypothesis” relates to organ specific safety; notably the upper gastrointestinal tract.

In discussions with the sponsor the division has emphasized the importance of rigorously testing the overall safety as well as upper gastrointestinal safety of valdecoxib. Given the evolving knowledge of selective COX-2 inhibition, this issue is of growing concern. This trial included a pre-defined basket of serious safety endpoints, called clinically relevant adverse events (CRAEs), which were to be formally adjudicated. In addition study 047 included renal safety endpoints in addition to asymptomatic endoscopically ascertained gastroduodenal ulcers as prespecified endpoints

ARTHRITIS:

The arthritis program consisted of early dose-ranging RCTs (Trials 15 and 16), followed by four standard efficacy trials (1 hip OA, 1 knee OA, and 2 RA), one active control, non-inferiority trial in OA (trial 63), and four formal safety trials – Trial 47 (OA/RA), 62 (RA), 48 (OA), and 53 (knee OA), all using a similar endoscopic ulcer primary endpoint, and one (47) also using a renal toxicity composite primary endpoint. These safety trials also collected validated efficacy endpoints, although not encompassing the full primary endpoint spectrum needed for formal efficacy evidence in OA or RA.

4-EFFICACY ANALGESIA:

The analgesia trials were assessed by (1) the improvement in pain over time, (2) the time to the onset of analgesia, and (3) the time to need for re-dosing or rescue medication. All three of these should be substantially inter-correlated, so all were tested at the $p < 0.05$ level, and no adjusting for multiplicity was done. However, this threefold endpoint approach was not appropriate for the morphine-sparing trials as they did not collect time to onset of analgesia, nor did they allow rescue medication. In these trials, two measures were used: (1) pain relief, and (2) morphine spared.

By the endpoints noted above, the following number of trials demonstrated efficacy (by either all three endpoints showing statistical significance at a $p < 0.05$ or two endpoints, in the case of the morphine-sparing trials): 10mg/d – 4 trials (#5, 14, 35, 24), 20mg/d - 8 trials (#5, 14, 35, 58, 59, 11, 24, 37), 40mg/d – 6 trials (35, 58, 59, 72, 24, 37). So few comparisons to active controls were statistically significantly different, either superior or inferior, that this evidence base is not further considered. Using the criteria of replicated success in two of the three pain models – dental pain, dysmenorrhea, and post-surgical pain, and excluding dosing at 80mg/d or 40mgbid – given evidence to suggest an unacceptable risk-benefit at these levels, the data support clear single-dose efficacy of 20mg, and 40mg. There was no replication of the efficacy of 10 mg based on pain intensity differences.

The clinical relevance of opioid-sparing was not adequately demonstrated. Pre-emptive administration of valdecoxib 20, 40 and 80 mg was associated with longer time to rescue medication compared with placebo in Trials 24 and 37 and number of patients who took rescue medication. Pre-emptive versus post operative dosing efficacy was not tested and peak pain intensity over 2 and 4 hours respectively in the two studies did not differ

between placebo and active treatment arms. Therefore the benefit of pre-emptive treatment is not clear, especially in view of the safety concerns in the post-operative setting.

ARTHRITIS:

The trials performed for the demonstration of efficacy in RA and OA were conventional and adequate in design. They included three formal efficacy trials in OA (two placebo control trials and one non-inferiority trial using only an active control, and two in RA, both placebo controlled. There were also safety RCTs with safety parameters as primary endpoints that also measured efficacy. These studies employed less standardized arthritis efficacy endpoints such as patient and investigator global assessments and time to dropout due to inefficacy.

The analysis of the efficacy results for RA and OA in this NDA were relatively straightforward. Valdecoxib did demonstrate efficacy at the 10mg and 20mg/d dosages in replicated data by usual comparisons with placebo arms, and there were no obvious threats (e.g. a differential dropout pattern) to the validity of these conclusions. Although no formal active control, non-inferiority evidence was pre-specified and pre-agreed upon in this NDA, this NDA, like others in the past, included numerous comparisons with active controls – and these were within the range of what has been seen with prior NDAs. There was no added benefit at 20mg/d, compared to 10mg/d.

5-SAFETY

Note: The review proper contains numerous adverse event tables which are supplied for reference, as the global safety experience of valdecoxib will likely bear critically on approval and labeling. Review comments are made in each section of these databases, but all relevant safety considerations are captured in the discussions of safety and risk / benefit here in the Executive Summary.

With two notable exceptions – edema and hypertension, valdecoxib was comparable to the standard non-steroidal agents used as active controls in the trials, except for some evidence supporting fewer GI adverse events, and some lessening of opiate side effects (e.g. constipation, dizziness, etc.) in trials with those as active controls. These findings will be reflected in the AE tables in the label. The finding of a greater incidence of edema and hypertension at doses above 20 mg/day, almost uniformly in the databases and clearly when prospectively addressed in formal safety Trials 47 and 62, is of concern, The relationship

between these events and the signal of more vascular events at 40mgbid dosing in the predisposed population of Trial 35 (CABG) is unclear. The excess of serious cardiovascular thromboembolic events in the valdecoxib arm of the CABG trial (see analgesic safety table #12) is of note as the entire study population received prophylactic low dose aspirin as part of the standard of care in this setting to minimize just such events. Given the emerging concern over a possible pro-thrombotic action of certain agents in the COX2 class, these data are of concern. These findings were seen at high dose in the peri-operative setting, not in the chronic safety studies of similar high doses.

REVIEW PROPER

SAFETY REREPORT ON TRIAL 35

This analgesia study comparing paracetamol/valdecoxib and placebo in patients undergoing CABG surgery was designed to test opioid-sparing, as reported in the Analgesia Efficacy section of this review. This trial was also specifically designed to test a safety hypothesis, using a pre-defined basket of safety endpoints, called "clinically relevant adverse events" (CRAEs), which included many serious vascular endpoints. The trial was powered using both a morphine sparing and a CRAE event rate calculation. In the trial analysis, there were 80 such events (25.7%) in the 311 paracetamol/valdecoxib patients, compared with 23 (15.2%) in the 151 placebo patients ($p=0.012$, by Fisher's Exact). The patient numbers for the particular events are shown in Table 1 below.

Note: The reader is also referred to an in depth analysis of this important trial in the Parecoxib Medical Review by James Witter M.D. PhD. It is attached *in toto* in the appendix.

Table 1: Clinically Relevant Adverse Events (CRAEs): Prespecified Endpoint event placebo

para/valdecoxib	
deaths	0 4
myocardial infarction	1 1
cerebrovascular accident	1 9
deep venous thrombosis	0 3
pulmonary embolism	0 2
congestive heart failure	1 4
renal dysfunction / failure	7 29
infection	11 29
pulmonary complication	4 19
pericarditis	1 4
GI event	0 4
major non-GI bleed	2 0

Discussion: These data, along with the other analyses in Dr. Witter's review (appendix) are manifestations of an increase in vascular events rates, which coupled with the signals seen elsewhere in this database (for example, Trial 47 and the adverse event tables shown later in this review) all contributes to the concern that there may be a component of increased thrombogenicity associated with this agent.

DEATHS

A total of 22 deaths have been reported in the NDA and the 120-Day Update. Fifteen occurred during a blinded trial, five in open extensions, and two in an ongoing cancer pain trial (Trial 40) which remains blinded.

study	DB/Open	age/sex	rx	duration	cause	post ?
16	DB	72/M	val 10mg	1d	ASCVD	yes
16	DB	78/F	val 5mg	11d	suspect cardiac arrest	no
16	DB	79/F	val 10mg	45d	trauma	?
48	DB	77/F	ibu	57d	complication-AVR	no
53	DB	77/M	val 5mg	11d	vent. fibrillation	no
53	DB	87/M	nap	69d	MVA	no
35	DB	58/M	para/val	2d	duodenal ulcer	yes
35	DB	69/F	para/val	10d	probable MI	yes
35	DB	67/M	para/val	7d	sepsis, wound infection, pneumonia	yes
35	DB	62/M	para/val	4d	massive hem. CVA	no
62	DB	79/F	val 20mg	15d	pulm. embolism	yes
62	DB	74/M	val 20mg	20d	GI bleed	yes
62	DB	64/F	val 20mg	98d	lymphoma, sepsis	no
62	DB	72/M	val 20mg	76d	metastatic lung CA	no
63	DB	74/F	diel	135d	MI	no
67	open	78/F	val 40mg	145d	CABG, pulm. infarct/hemorrhage	yes
67	open	67/M	val 40mg	81d	"abdominal mass"	no
67	open	45/M	val 40mg	305d	bilat. pulm. emboli	yes
67	open	72/F	val 40mg	317d	pulm. fibrosis	no
67	open	60/M	val 40mg	297d	unknown	no
40	DB	71/M	(blinded)	38d	met. adenoCA	?
40	DB	50/F	(blinded)	6d	met. breast CA	?

Deaths

The total double-blind exposure for all doses of valdecoxib is 1283 patient-years (107, 323,397,316, 142 patient-years for 1-5mg, 10mg, 20mg, 40mg, and 80mg valdecoxib total daily dose, respectively) , compared to 291 patient-years for naproxen, 248 patient-years for diclofenac, 40 patient-years for ibuprofen, and 161 patient-years for placebo. Thus, the crude death rate in the unblinded controlled studies for valdecoxib is 0.9% (12/1283) compared to 0.52% (3/579) in comparator NSAIDs (p=NS, by Fisher's Exact). Given the 2:1 (parecoxib/valdecoxib: placebo) randomization in the CABG trial the 4 deaths in that study may bias the rates. This study was in an enriched population for serious cardiovascular adverse events and used a dose not proposed for chronic use. The rates excluding this trial are 0.6% for valdecoxib compared to 0.5% for the NSAID comparators.

The rate of cardiovascular thromboembolic deaths (including arrhythmia, MI and PVD) in the controlled database was 0.5% (6/1283) for valdecoxib and 0.3% (2/579) for the NSAID groups combined. Excluding the CABG study the rates for such events was 0.3% (4/1283) for valdecoxib and 0.3% for NSAID comparators. The number of events was small and there was no pattern seen based on dose or duration of therapy. Excluding the CABG trial there was no clear signal for differences in event rates between valdecoxib and comparator NSAIDs. A large outcome study employing chronic dose therapy would be needed to address this issue further. Such as study would include overall safety

including cardiovascular, renal and GI endpoints as well as overall deaths and serious adverse events.

Requested Cardiovascular Safety Analysis in High Risk Patients

Concerns have been raised regarding COX-2 selective agents and cardiovascular safety following outcome study (VIGOR) of one such agent. Based on these concerns a subanalysis of cardiovascular events in high risk patients was requested by the reviewer. The following tables do not suggest a higher risk of cardiovascular events in an enriched population of “high risk” or “at risk” patients for valdecoxib compared to the NSAID comparators. The small number of patients exposed precludes robust comparisons.

HIGH RISK PATIENTS*: Rates of Serious Thromboembolic Cardiovascular Adverse Events**

Adverse Event	Placebo	Valdecoxib (10 mg)	Valdecoxib (20 mg)	Valdecoxib (40 mg)	Valdecoxib (80 mg)	NSAIDs
n	106	174	144	93	42	248
Exposure (patient yrs.)	12.5	49.4	46.8	22.7	11.5	71.3
Events	2	3	1	1	1	6
Incidence (%)	1.9	1.7	0.7	1.1	2.4	2.4
Events/100 pt yr	16.0	6.1	2.0	4.4	8.7	8.4

* Patients with history of angina, CAD, MI, and CVA in studies 015, 016, 047, 048, 049, 053, 060, 061, 062, 063.

** FDA defined, including MI, myocardial ischemia, unstable angina, cardiac arrest, sudden cardiac death, CVA/TIA, PE, venous thrombosis, embolism, peripheral gangrene, and peripheral ischemia.

AT RISK PATIENTS*: Rates of Serious Thromboembolic Cardiovascular Adverse Events**

Adverse Event	Placebo	Valdecoxib (10 mg)	Valdecoxib (20 mg)	Valdecoxib (40 mg)	Valdecoxib (80 mg)	NSAIDs
n	503	665	773	646	258	1144
Exposure (patient yr.)	72.7	197.8	261.9	186.7	93.2	356.5
Events	0	1	4	3	1	7
Incidence (%)	0.0	0.2	0.5	0.5	0.4	0.6
Events/100 pt. yr	0.0	0.5	1.5	1.6	1.1	2.0

* Patients with a history of hypertension, hyperlipidemia, or smoking (but not angina, CAD, MI, or CVA) in same studies as in above table

* same as above table

ARTHRITIS SAFETY TABLE 13: SERIOUS ADVERSE EVENTS (NUMBERS) IN TRIALS 15/16(6wk) and 48/49/53/60/61(3mo)

Dose (mg/d)	Placebo	1-5 mg	10 mg	20 mg	40 mg	NSAIDs
No. treated	1142	818	1284	1012	430	1347
Overall percentage of any event	2.4	1.7	1.6	1.6	1.6	2.1
Any event	27/38	14/17	20/35	16/24	7/12	28/44
Autonomic Nervous System Disorders						
Overall percentage	0.0	0.0	0.0	1.0	0.5	0.0
Hypertension aggravated					2/2	
Body as a Whole – General Disorders						
Overall percentage	0.5	0.5	0.5	<0.1	0.5	0.2
Back pain	2/2		1/1			1/1
Injury – accidental			2/4			1/1
Treatment-emergent surgery	1/1		2/2			
Disorders, Female						
Overall percentage	0.3	0.2		0.3		0.1
Breast neoplasm malignant female	1/1			2/2		
Gastrointestinal System Disorders						
Overall percentage	0.4	0.1	0.2	<0.1	0.2	0.5
Abdominal pain	1/1		1/1			2/2
Diverticulitis	2/2					1/1
Gastric ulcer						2/2
Gastritis	1/1					2/2
Musculoskeletal System Disorders						
Overall percentage	0.0	0.2	<0.1	<0.1	0.0	0.0
Fracture accidental		2/2	1/1			
Myo, Endo, Pericardial and Valve Disorders						
Overall percentage	0.2	0.4	0.2	0.3	0.2	0.6
Angina pectoris	1/1					2/2
Coronary artery disorder	2/2		1/1	1/1		5/5
Myocardial infarction	1/1	3/3	3/3	1/1	1/1	2/2
Respiratory System Disorders						
Overall percentage	0.5	0.2	0.5	0.3	0.0	<0.1
Pneumonia	2/2		4/4			
Vascular (Extracardiac) Disorders						
Overall percentage	<0.1	0.0	0.0	<0.1	0.5	<0.1
Cerebrovascular disorder	1/1			1/1	2/2	2/2

For specific adverse events, values represent number of patients with a serious adverse event / number of episodes. Episodes can represent multiple, different serious adverse event or multiple occurrences of the same serious adverse event. Only non-zero values are shown except for percentages.

ARTHRITIS SAFETY TABLE 14: PATIENT LISTING OF SERIOUS ADVERSE EVENTS OF UNCERTAIN OR PROBABLE RELATION TO STUDY DRUG IN TRIALS 15/16(6wk) and 48/49/53/60/61(3mo)

Study/Patient ID/Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity/ Relationship	DER Number
015/US0032-0450/ PBO	54/ M	30	33	Abdominal pain	Mod/Uncertain	971222-CL326
015/US0033-0462/ NAP	62/ M	10 10	10 (O) 10 (O)	Gastric Ulcer [†] Gastritis [†]	Severe/Probable Severe/Probable	971212-CL430
048/US0038-0231/ DIC	59/F	47	50	Pancreatitis	Severe/Uncertain	990715-CL929
048/US0046-1154/ DIC	71/F	23 25	25 28	Abdominal pain [†] Gastritis	Severe/Uncertain Mild/Uncertain	991102-CL242 000218-CL193
048/US0051-1118/ DIC	62/F	70 70	73 73	Diarrhea [†] Hematochezia [†]	Severe/Probable Severe/Probable	991215-CL470
048/US0078-1059/ DIC	53/F	85	85 (O)	Hepatic function abnormal	Mild/Probable	991112-CL774
048/US0085-1205/ DIC	68/ M	32 32	56 56	Coronary artery disorder Myocardial ischemia	Severe/Uncertain Severe/Uncertain	000104-CL310
048/US0086-0720/ V10	73/F	52	52 (O)	Anemia	Mild/Uncertain	991026-CL712
049/US0010-0173/ V10	78/F	68	74	Nausea	Mod/Uncertain	990820-CL716
049/US0108-0427/ NAP	50/F	37 40	39 40 (O)	Chest pain non-cardiac Abdominal pain [†]	Mod/Probable Mod/Probable	990817-CL537
053/CA0016- 0884/V20	63/ M	78	78	Dyspnea	Severe/Probable	991123-CL234
053/US0114-1173/ V20	61/F	30 33 33	33 (O) 33 (O) 33 (O)	Chest pain non-cardiac Palpitation [†] Myalgia	Severe/Uncertain Severe/Uncertain Mod/Uncertain	000211-CL770
060/US0120-1511/ V20	73/F	9 9 9	15 15 15	Ileus [†] Nausea [†] Vomiting [†]	Severe/Uncertain Severe/Uncertain Severe/Uncertain	000210-CL621
060/US0436-1358/ V40	57/ M	69	69	Myocardial infarction	Severe/Uncertain	000424-CL329
061/US0115-1454/ NAP	52/ M	53 53	55 55	Gastric Ulcer GI Hemorrhage [†]	Severe/Probable Severe/Probable	000419-CL479
061/050115-1455/ V40	62/F	46 49	46 49 (O)	GI Hemorrhage [†] Anemia [†]	Severe/Probable Severe/Probable	000502-CL414
061/US0534-1094/ PBO	77/F	22	25	Chest pain	Severe/Uncertain	000310-CL633

[†]Patient prematurely withdrew due to this adverse event. Mod; moderate; PBO, placebo; NAP, naproxen sodium; DIC, diclofenac; V10, valdecoxib 10 mg total daily dose; V20, valdecoxib 20 mg total daily dose; V40, valdecoxib 40 mg total daily dose; O, ongoing (on date of last dose).

Patient Number	Serious Adverse Event (Preferred Term)	Treatment	Caused Withdrawal	Relationship to Study Drug
GE0010-0508	Hypertension Aggravated	Diclofenac 75 mg BID	No	None
FR0008-0385	Hypertension Aggravated	Valdecoxib 20 mg QD	Yes	Probable
HU0003-0581	Hypertension Aggravated	Valdecoxib 40 mg QD	No	Uncertain
Body as a Whole				
GE0010-1138	Back Pain	Valdecoxib 20 mg QD	Yes	None
BE0004-0513	Back Pain	Diclofenac 75 mg BID	Yes	None
PL0005-0731	Injury Accidental	Valdecoxib 20 mg QD	No	None
GE0003-0461	Injury Accidental	Diclofenac 75 mg BID	No	None
CO0004-1819	Pain	Diclofenac 75 mg BID	Yes	None
CZ0003-0713	Previously Scheduled Surgery	Diclofenac 75 mg BID	No	None
FI0003-1212	Previously Scheduled Surgery	Diclofenac 75 mg BID	No	None
HU0004-1224	Respite Care	Diclofenac 75 mg BID	No	None
Central and Peripheral Nervous System Disorders				
HU0003-0581	Ataxia	Valdecoxib 40 mg QD	No	Uncertain
HU0003-0581	Dizziness	Valdecoxib 40 mg QD	No	Uncertain
CO0004-1819	Headache	Diclofenac 75 mg BID	Yes	None
HU0003-0581	Headache	Valdecoxib 40 mg QD	No	Uncertain
FR0004-0483	Neuralgia	Valdecoxib 40 mg QD	No	None
SZ0003-1375	Neuralgia	Diclofenac 75 mg BID	Yes	None
Collagen Disorders				
IT0001-0793	Arthritis Rheumatoid Aggravated	Valdecoxib 20 mg QD	No	None
NE0004-1146	Arthritis Rheumatoid Aggravated	Valdecoxib 40 mg QD	Yes	None
NE0004-1154	Arthritis Rheumatoid Aggravated	Valdecoxib 40 mg QD	Yes	None
PL0004-0724	Arthritis Rheumatoid Aggravated	Valdecoxib 40 mg QD	Yes	None
Female Disorders				
HU0004-0595	Breast Neoplasm Malignant Female	Valdecoxib 40 mg QD	Yes	None
UK0001-0050	Breast Neoplasm Malignant Female	Valdecoxib 20 mg QD	No	None
SK0004-0753	Menstrual Disorder	Diclofenac 75 mg BID	No	None
SK0004-0753	Uterine Fibroid	Diclofenac 75 mg BID	No	None
Endocrine Disorders				
DE0003-0362	Hyperparathyroidism	Valdecoxib 20 mg QD	No	None

Patient Number	Serious Adverse Event (Preferred Term)	Treatment	Caused Withdrawal	Relationship to Study Drug
HU0004-1222	Parathyroid Disorder	Valdecoxib 40 mg QD	No	None
Gastrointestinal System Disorders				
IS0001-0556	Abdominal Pain	Valdecoxib 40 mg QD	Yes	Probable
CO0004-1819	Abdominal Pain	Diclofenac 75 mg BID	No	None
DE0002-0889	Abdominal Pain	Diclofenac 75 mg BID	No	None
FR0002-0411	Abdominal Pain	Diclofenac 75 mg BID	No	None
PL0002-0744	Abdominal Pain	Diclofenac 75 mg BID	Yes	Probable
PL0003-0748	Abdominal Pain	Diclofenac 75 mg BID	No	Uncertain
CZ0004-0693	Colitis Ulcerative	Diclofenac 75 mg BID	Yes	None
CO0004-1819	Diarrhea	Diclofenac 75 mg BID	No	None
DE0002-0889	Diarrhea	Diclofenac 75 mg BID	No	None
PL0004-1256	Duodenal Ulcer	Valdecoxib 20 mg QD	Yes	Probable
CZ0004-0693	Duodenal Ulcer	Diclofenac 75 mg BID	Yes	Uncertain
PL0005-0687	Duodenal Ulcer	Diclofenac 75 mg BID	No	Probable
CO0004-1826	Esophagitis	Diclofenac 75 mg BID	Yes	Probable
PL0002-0744	Gastric Ulcer	Diclofenac 75 mg BID	Yes	Probable
PL0005-0686	Gastric Ulcer	Diclofenac 75 mg BID	No	Probable
PL0005-0732	Gastric Ulcer	Diclofenac 75 mg BID	No	Probable
CZ0005-0698	Gastric Ulcer Hemorrhagic	Diclofenac 75 mg BID	No	Probable
FR0008-0386	Gastritis	Valdecoxib 40 mg QD	Yes	Probable
GE0005-0459	Gastritis	Valdecoxib 20 mg QD	Yes	Probable
GE0005-0462	Gastritis	Valdecoxib 20 mg QD	Yes	Probable
HU0008-0594	Gastritis	Valdecoxib 40 mg QD	Yes	Probable
NO0003-1468	Gastritis	Diclofenac 75 mg BID	Yes	Probable
CO0004-1819	Gastroenteritis	Diclofenac 75 mg BID	No	None
CO0003-1836	Gastroenteritis	Diclofenac 75 mg BID	No	None
BE0005-0471	GI Hemorrhage	Valdecoxib 20 mg QD	Yes	Probable
PL0002-0744	GI Hemorrhage	Diclofenac 75 mg BID	Yes	Probable
FI0003-1184	Hematochezia	Diclofenac 75 mg BID	No	Probable

Patient Number	Serious Adverse Event (Preferred Term)	Treatment	Caused Withdrawal	Relationship to Study Drug
FI0003-1184	Hematochezia	Diclofenac 75 mg BID	Yes	Probable
IS0001-0556	Nausea	Valdecoxib 40 mg QD	Yes	Probable
CO0004-1819	Nausea	Diclofenac 75 mg BID	No	None
CO0004-1819	Vomiting	Diclofenac 75 mg BID	No	None
IS0001-0556	Vomiting	Valdecoxib 40 mg QD	Yes	Probable
NO0003-1468	Vomiting	Diclofenac 75 mg BID	Yes	Probable
Heart Rate and Rhythm Disorders				
FR0004-0426	Arrhythmia	Diclofenac 75 mg BID	Yes	Uncertain
CZ0005-0698	Tachycardia Supraventricular	Diclofenac 75 mg BID	No	None
Liver and Biliary System Disorders				
IS0001-0561	Cholecystitis	Valdecoxib 20 mg QD	No	None
IS0001-0561	Cholelithiasis	Valdecoxib 20 mg QD	No	None
CO0004-1819	SGOT Increased	Diclofenac 75 mg BID	No	Uncertain
CO0004-1819	SGPT Increased	Diclofenac 75 mg BID	No	Uncertain
Metabolic and Nutritional Disorders				
AU0003-0324	Dehydration	Valdecoxib 40 mg QD	Yes	Probable
Musculoskeletal System Disorders				
CO0004-1819	Arthrosis	Diclofenac 75 mg BID	Yes	None
SZ0004-1398	Arthrosis	Valdecoxib 20 mg QD	Yes	None
HU0005-0617	Fracture Accidental/ Accident Hospitalization	Valdecoxib 40 mg QD	No	None
HU0005-0617	Fracture Accidental/ Fixation of Clavicle and AC Joint	Valdecoxib 40 mg QD	No	None
PL0005-0731	Fracture Accidental/ Fracture of Right Elbow	Valdecoxib 20 mg QD	No	None
PL0005-0731	Fracture Accidental/ Fracture of Right Radius	Valdecoxib 20 mg QD	No	None
BR0001-1803	Synovitis	Diclofenac 75 mg BID	No	None
Myo-, Endo-, Pericardial, and Valve Disorders				
PL0004-1257	Myocardial Infarction	Diclofenac 75 mg BID	Yes	None
NE0004-1147	Myocardial Infarction	Valdecoxib 40 mg QD	No	None
Neoplasm				
IT0001-0793	GI Neoplasm Malignant	Valdecoxib 20 mg QD	No	None
PL0001-0735	Neoplasm	Valdecoxib 40 mg QD	No	None
SA0005-0124	Pulmonary Carcinoma	Valdecoxib 20 mg QD	Yes	None
Platelet, Bleeding, and Clotting Disorders				

Patient Number	Serious Adverse Event (Preferred Term)	Treatment	Caused Withdrawal	Relationship to Study Drug
AU0002-0314	Embolism Pulmonary	Valdecoxib 20 mg QD	No	None
31.1.1. Red Blood Cell Disorders				
AU0002-0314	Pancytopenia	Valdecoxib 20 mg QD	No	None
Resistance Mechanism Disorders				
FI0003-1185	Infection	Valdecoxib 40 mg QD	No	None
PL0005-0727	Infection Bacterial	Valdecoxib 40 mg QD	Yes	None
AU0002-0314	Sepsis	Valdecoxib 20 mg QD	No	None
AU0013-0848	Infection soft tissue	Diclofenac 75 mg BID	No	None
Respiratory System Disorders				
PL0003-0750	Bronchitis	Diclofenac 75 mg BID	No	None
SA0005-0134	Bronchitis	Diclofenac 75 mg BID	No	None
GE0005-0462	Pneumonia	Valdecoxib 20 mg QD	No	None
IS0002-0548	Pneumonia	Valdecoxib 40 mg QD	Yes	None
NZ0006-0335	Pneumonia	Valdecoxib 40 mg QD	No	None
SA0002-0142	Pneumonia	Valdecoxib 40 mg QD	No	None
CO0004-1825	Pneumonia Lobar	Valdecoxib 40 mg QD	No	None
SA0002-0142	Pneumonitis	Valdecoxib 40 mg QD	Yes	None
DE0002-0889	Sinusitis	Diclofenac 75 mg BID	No	Uncertain
AU0003-0324	Upper Respiratory Tract Infection	Valdecoxib 40 mg QD	No	None
Skin and Appendages Disorders				
NO0004-1472	Skin Disorder	Valdecoxib 40 mg QD	No	None
Urinary System Disorders				
PL0001-0737	Hematuria	Valdecoxib 40 mg QD	Yes	None
PL0001-0737	Renal Calculus	Valdecoxib 40 mg QD	Yes	None
AU0002-0314	Renal Failure Acute	Valdecoxib 20 mg QD	No	None
PO0002-0799	Renal Pain	Diclofenac 75 mg BID	No	Uncertain
Vascular (Extracardiac) Disorders				
HU0004-0598	Cerebrovascular disorder	Diclofenac 75 mg BID	No	None
Vision Disorders				
BE0006-0466	Vision Abnormal	Diclofenac 75 mg BID	No	None
White Cell and RES Disorders				
IT0001-0793	Lymphoma-like Disorder	Valdecoxib 20 mg QD	No	None

Derived from Table T33, Appendix 3.4, and Appendix 3.7.2.

ARTHRITIS SAFETY TABLE 18: PATIENT LISTING: SERIOUS ADVERSE EVENTS IN DOUBLE-BLIND PORTION OF TRIAL 63 (6mo) - OSTEOARTHRITIS

Patient Number	Serious Adverse Event (Preferred Term)	32. TREATMENT GROUP	Caused Withdrawal	Relationship to Study Drug
Autonomic Nervous System Disorders				
3162	Encephalopathy Hypertensive	Valdecoxib 10 mg QD	No	None
3224	Vasospasm	Valdecoxib 20 mg QD	No	None
3690	Syncope	Diclofenac 75 mg BID	No	Uncertain
3966	Hypotension Postural	Diclofenac 75 mg BID	No	None
3966	Syncope	Diclofenac 75 mg BID	No	None
4024	Hypertension Aggravated	Valdecoxib 20 mg QD	No	Uncertain
4333	Hypertension	Valdecoxib 20 mg QD	Yes	Uncertain
Body as a Whole – General Disorders				
3009	Sudden Death	Diclofenac 75 mg BID	Yes	None
3182	Treatment Emergent Surgery	Diclofenac 75 mg BID	No	None
3242	Previously Scheduled Surgery	Valdecoxib 10 mg QD	No	None
3242	Previously Scheduled Surgery	Valdecoxib 10 mg QD	No	None
3371	Treatment Emergent Surgery	Valdecoxib 20 mg QD	No	None
3388	Treatment Emergent Surgery	Valdecoxib 10 mg QD	No	None
3437	Treatment Emergent Surgery	Valdecoxib 20 mg QD	No	None
3486	Treatment Emergent Surgery	Valdecoxib 20 mg QD	Yes	None
3520	Chest Pain Non-Cardiac	Valdecoxib 10 mg QD	No	None
3562	Injury-Accidental	Valdecoxib 10 mg QD	No	None
3676	Treatment Emergent Surgery	Diclofenac 75 mg BID	No	None
3685	Treatment Emergent Surgery	Valdecoxib 20 mg QD	No	None
3874	Cyst, NOS	Diclofenac 75 mg BID	No	None
3982	Treatment Emergent Surgery	Valdecoxib 20 mg QD	No	None
4008	Treatment Emergent Surgery	Diclofenac 75 mg BID	No	None
4028	Treatment Emergent Surgery	Valdecoxib 10 mg QD	Yes	None
4058	Injury-Accidental	Valdecoxib 10 mg QD	Yes	None
Cardiovascular Disorders, General				
3268	Cardiac Failure	Diclofenac 75 mg BID	Yes	Uncertain
3544	Unstable Angina	Diclofenac 75 mg BID	No	None
4274	Cardiac Failure	Diclofenac 75 mg BID	Yes	Uncertain
4448	Aneurysm	Valdecoxib 20 mg QD	Yes	None
Central and Peripheral Nervous System Disorders				
3085	Neuralgia	Valdecoxib 10 mg QD	No	None
Endocrine Disorders				
4033	Gynecomastia	Diclofenac 75 mg BID	No	None
Fetal Disorders				
3504	Exophthalmos	Diclofenac 75 mg BID	No	None
4275	Hernia Congenital	Valdecoxib 10 mg QD	No	None
Gastro-intestinal System Disorders				
3055	Melena	Valdecoxib 20 mg QD	Yes	Probable
3160	Abdominal Pain	Valdecoxib 20 mg QD	No	None
3340	Abdominal Pain	Diclofenac 75 mg BID	Yes	Probable
3370	Gastritis	Valdecoxib 20 mg QD	Yes	Probable
3370	Hematemesis	Valdecoxib 20 mg QD	Yes	Probable
3403	Gastric Ulcer Hemorrhagic	Valdecoxib 20 mg QD	No	Uncertain
3504	Hernia	Diclofenac 75 mg BID	No	None
3674	Duodenal Ulcer	Diclofenac 75 mg BID	No	Probable
3674	Gastric Ulcer	Diclofenac 75 mg BID	No	Probable
3674	Esophagitis	Diclofenac 75 mg BID	No	Probable

3702	Gastric Ulcer	Diclofenac 75 mg BID	Yes	Probable
3718	Diarrhea	Diclofenac 75 mg BID	No	Uncertain
3718	Gastric Ulcer	Diclofenac 75 mg BID	Yes	Probable
3950	Anal Fissure	Valdecoxib 20 mg QD	No	None
4278	Peritonitis	Valdecoxib 10 mg QD	Yes	None
4292	Abdominal Pain	Diclofenac 75 mg BID	No	Probable
4292	Gastric Ulcer	Diclofenac 75 mg BID	Yes	Probable
4296	Gastric Ulcer	Diclofenac 75 mg BID	Yes	Probable
4339	Gastric Ulcer Hemorrhage	Valdecoxib 20 mg QD	Yes	Probable
4346	Diarrhea	Diclofenac 75 mg BID	No	Probable
4346	Diarrhea	Diclofenac 75 mg BID	Yes	Probable
4449	Abdominal Pain	Valdecoxib 10 mg QD	Yes	Probable
4449	Abdominal Pain	Valdecoxib 10 mg QD	Yes	Probable
4449	Gastric Ulcer	Valdecoxib 10 mg QD	Yes	Probable
4456	Gastritis	Diclofenac 75 mg BID	Yes	Probable
4456	Gastritis	Diclofenac 75 mg BID	Yes	Probable
4456	Dyspepsia	Diclofenac 75 mg BID	Yes	Probable
4507	Abdominal Pain	Valdecoxib 20 mg QD	No	None
Heart Rate and Rhythm Disorders				
3707	Bradycardia	Diclofenac 75 mg BID	No	None
3707	Arrhythmia Ventricular	Diclofenac 75 mg BID	No	None
4274	Fibrillation Atrial	Diclofenac 75 mg BID	No	None
Metabolic and Nutritional Disorders				
3164	Diabetes Mellitus	Valdecoxib 20 mg QD	No	None
3690	Hypoglycemia	Diclofenac 75 mg BID	No	None
Musculo-Skeletal System Disorders				
3088	Fracture Accidental	Diclofenac 75 mg BID	Yes	None
3475	Arthritis Aggravated	Valdecoxib 10 mg QD	Yes	None
3493	Arthrosis	Diclofenac 75 mg BID	No	None
3518	Fracture Accidental	Valdecoxib 20 mg QD	No	None
3529	Arthritis Aggravated	Valdecoxib 10 mg QD	No	None
3544	Tendon Disorder	Diclofenac 75 mg BID	No	
3557	Fracture Accidental	Diclofenac 75 mg BID	No	None
3946	Arthritis Aggravated	Valdecoxib 10 mg QD	Yes	None
4008	Fracture Accidental	Diclofenac 75 mg BID	No	None
4008	Tendon Disorder	Diclofenac 75 mg BID	No	None
4305	Arthritis	Valdecoxib 10 mg QD	No	None
Myo Endo Pericardial & Valve Disorders				
3158	Myocardial Infarction	Diclofenac 75 mg BID	Yes	None
3377	Myocardial Infarction	Diclofenac 75 mg BID	No	None
3398	Angina Pectoris	Valdecoxib 20 mg QD	Yes	None
4026	Myocardial Infarction	Diclofenac 75 mg BID	Yes	None
4274	Myocardial Infarction	Diclofenac 75 mg BID	No	None
Neoplasm				
3143	Breast Neoplasm Malignant Female	Valdecoxib 20 mg QD	No	None
3310	Neoplasm	Valdecoxib 10 mg QD	No	None
4278	Ovarian Cyst Malignant	Valdecoxib 10 mg QD	Yes	None
4306	Breast Neoplasm Malignant Female	Valdecoxib 10 mg QD	Yes	Uncertain
Psychiatric Disorders				
3966	Depression	Diclofenac 75 mg BID	No	None
Red Blood Cell Disorders				
3707	Anemia	Diclofenac 75 mg BID	No	None
Reproductive Disorders, Female				
3231	Vaginal Hemorrhage	Diclofenac 75 mg BID	No	None
3231	Endometrial Hyperplasia	Diclofenac 75 mg BID	No	None
Reproductive Disorders, Male				
4458	Prostatic Disorder	Valdecoxib 10 mg QD	No	None

Resistance Mechanism Disorders				
3388	Infection	Valdecoxib 10 mg QD	No	None
3442	Infection	Diclofenac 75 mg BID	Yes	None
Respiratory System Disorders				
3370	Pneumonia	Valdecoxib 20 mg QD	No	
3484	Bronchitis	Diclofenac 75 mg BID	No	None
3874	Laryngitis	Diclofenac 75 mg BID	No	None
4076	Dyspnea	Diclofenac 75 mg BID	No	Uncertain
Skin and Appendages Disorders				
3164	Nail Disorder	Valdecoxib 20 mg QD	No	None
3544	Inflammation	Diclofenac 75 mg BID	No	None
Urinary System Disorders				
3208	Urinary Incontinence	Valdecoxib 10 mg QD	No	None
4029	Hematuria	Diclofenac 75 mg BID	No	None
4029	Benign Prostatic Hyperplasia	Diclofenac 75 mg BID	No	None
Vascular (Extracardiac) Disorders				
3027	Cerebrovascular Disorder	Diclofenac 75 mg BID	Yes	None
3417	Cerebrovascular Disorder	Valdecoxib 20 mg QD	No	None
3417	Hematoma NOS	Valdecoxib 20 mg QD	No	None
3421	Cerebrovascular Disorder	Diclofenac 75 mg BID	No	None
3447	Peripheral Vascular Disease	Valdecoxib 20 mg QD	No	None
3539	Cerebrovascular Disorder	Valdecoxib 20 mg QD	Yes	None
3556	Cerebrovascular Disorder	Valdecoxib 10 mg QD	No	None
3678	Peripheral Ischemia	Valdecoxib 10 mg QD	No	None
4061	Claudication Intermittent	Valdecoxib 10 mg QD	No	None
Vision Disorders				
3495	Cataract	Valdecoxib 20 mg QD	No	None
3495	Lacrimal Duct Obstruction	Valdecoxib 20 mg QD	No	None
3716	Cataract	Valdecoxib 20 mg QD	No	None
3716	Cataract	Valdecoxib 20 mg QD	No	None
3793	Retinal Detachment	Valdecoxib 10 mg QD	No	Uncertain

ARTHRITIS SAFETY TABLE 23: SERIOUS ADVERSE EVENTS (NUMBERS)

Adverse Event	Valdecoxib (Final TDD Dose)			
	10 mg	20 mg	40 mg	80 mg
No. treated	2044	1820	1267	394
Event rate per 100 patient-years	10.8	12.4	10.3	7.5
Autonomic Nervous System Disorders				
Overall percentage	0.3	0.7	0.5	0.7
Hypertension aggravated			2/2	
Ileus		3/3		
Body as a Whole –General Disorders				
Overall percentage	2.0	5.0	3.3	0.7
Back pain	2/2	5/5	3/3	
Injury – accidental	1/1	3/4	1/1	
Pain			2/2	
Treatment emergent surgery	¼	27/27	5/6	
Cardiovascular Disorders, General				
Overall percentage	0.0	0.9	0.2	0.7
Cardiac failure		7/7		1/1
Central and Peripheral Nervous System Disorders				
Overall percentage	0.3	0.9	0.2	0.0
Convulsions		2/2		
Disorders, Female				
Overall percentage	0.9	0.4	1.0	0.0
Uterine disorder NOS	1/1	2/2	1/1	
Gastrointestinal System Disorders				
Overall percentage	1.7	2.4	1.0	2.2
Abdominal pain	1/1	2/2		1/1
Gastritis		3/3	1/1	
Intestinal obstruction		2/2		1/1
Heart Rate and Rhythm Disorders				
Overall percentage	0.7	0.8	1.0	0.0
Bradycardia		2/2	1/1	
Fibrillation atrial	1/1	2/2	2/2	
Tachycardia			2/2	
Liver and Biliary System Disorders				
Overall percentage	0.3	0.3	0.7	0.0
Cholelithiasis	1/1		2/2	
Metabolic and Nutritional Disorders				
Overall percentage	0.3	0.4	0.2	0.7
Dehydration		2/2		1/1
Musculoskeletal System Disorders				
Overall percentage	0.3	0.9	0.5	0.0
Tendon disorder		3/3		
Myo, Endo, Pericardial and Valve Disorders				
Overall percentage	1.3	0.8	1.0	0.7
Angina pectoris	1/1	3/4	¾	1/1
Coronary artery disorder	1/1		2/2	

Adverse Event	Valdecoxib (Final TDD Dose)			
	10 mg	20 mg	40 mg	80 mg
Mitral insufficiency			2/2	
Myocardial infarction	1/1	2/2		1/1
Myocardial ischemia	2/2			
Platelet, Bleeding, and Clotting Disorders				
Overall percentage	0.3	0.1	0.5	0.0
Embolism pulmonary	1/1		2/2	
Respiratory System Disorders				
Overall percentage	2.4	0.8	1.4	0.7
Dyspnea			3/4	
Pneumonia	2/2	2/2	2/3	1/1
Pulmonary edema		2/2		
Urinary System Disorders				
Overall percentage	0.0	0.7	0.7	0.0
Cystitis		2/2		
Urinary incontinence		2/2	1/1	
Vascular (Extracardiac) Disorders				
Overall percentage	0.7	0.9	1.0	0.0
Cerebrovascular disorder	2/2	4/4	2/2	

ARTHRITIS SAFETY TABLE 24: PATIENT LISTING OF SERIOUS ADVERSE EVENTS PROBABLY RELATED TO STUDY DRUG

Patient ID/ Treatment	Age/ Sex	Day of Onset	Day of Resolution	Preferred Term	Severity/ Relationship	DER Number
00070025/V20	71/F	167	169	Bronchospasm	Severe/Uncertain	990820- CL.707
00100003/V20	79/F	53	56	Cardiac failure [†]	Severe/Uncertain	990210- CL.662
00120055/V10	69/F	54	56	GI hemorrhage [†]	Severe/Uncertain	990414- CL.859
00140006/V20	57/ M	152 152 152 152	158 168 158 158	Anemia Diverticulosis [†] Doudenitis GI hemorrhage	Severe/Uncertain Severe/Uncertain Severe/Uncertain Severe/Uncertain	990628- CL.798
00160029/V20	55/F	233	236 (O)	Gastric ulcer [†]	Severe/Probable	991011- CL.160
00180038/V20	64/ M	211	233 (O)	Cardiac failure [†]	Severe/Uncertain	000317- CL.536
00180039/V10	68/F	282	285	Emphysema	Severe/Uncertain	000421- CL.204
00210024/V20	67/F	48	63	Creatine phosphokinase increased	Moderate/Probable	990413- CL.152
00220014/V20	79/ M	137 137	137 (O) 137 (O)	Gastritis [†] Diverticulitis [†]	Severe/Uncertain Severe/Uncertain	990623- CL.547
1406/V80	52/ M	195 197 173	195 198 178	Syncope [†] Syncope [†] Bradycardia	Severe/Uncertain Severe/Uncertain Severe/Uncertain	000620- CL.679 000628- CL.342 000605- CL.117
01200602 [#] /V20	70/F	128	146 (O)	Hepatic function abnormal [†]	Severe/Uncertain	000330- CL.304
02670554/V80	77/ M	2	2	Chest pain	Severe/Probable	000609- CL.444
0464/V80	58/ M	89	UNK	Gastric ulcer hemorrhagic [†]	Severe/Probable	000713- CL.562
0554/V80	77/ M	2	2	Chest pain	Severe/Probable	000609- CL.444
04020700/V40	69/ M	151	(O)	Hypertension aggravated	Severe/Probable	001012- CL.313
05050859 [#] /V40	63/ M	187	187 (O)	Embolism pulmonary [†]	Severe/Uncertain	000531- CL.034
05051087/V40	73/F	65 71	83 71 (O)	Gastritis [†] Duodenal ulcer [†]	Mod/Uncertain Mod/Uncertain	000627- CL.886
05280925/V20	56/ M	18 18	22 22	Angina pectoris Gastritis	Severe/Uncertain Severe/Uncertain	000207- CL.259 000207- CL.964
05751524/V40	72/F	65	65 (O)	Embolism pulmonary [†]	Severe/Uncertain	000620- CL.656

[†]Patient prematurely withdrew due to this adverse event. [#]Patient in extended exposure cohort. Mod; moderate; V10, valdecoxib 10 mg total daily dose; V20, valdecoxib 20 mg total daily dose; V40, valdecoxib 40 mg total daily dose; V80, valdecoxib 80 mg total daily dose; O, ongoing (on date of last dose), UNK, unknown.

*Onset 3 days after final dose.

