I. Introduction:

The following review summarizes the safety data for NDA 21-389 submitted by Merck, for the drug etoricoxib. It focuses on safety data provided from both the primary NDA as well as data from the 7000 patient EDGE study which will be reported separately. The review presents mortality data, followed by an analysis of CV events, GI events, and lastly by renal events. In each section, data will be presented from the NDA proper which includes safety data from all chronic studies (no data from acute studies will be provided here). This includes data from the following indications: OA, RA, CLBP, AS, as well as from endoscopy studies.

The following comparisons will be presented:
a. Etoricoxib vs placebo (includes studies which contained placebo as the comparator, with studies up to 12 weeks in duration)
b. Etoricoxib vs naproxen (includes all studies with naproxen as the comparator, and for any length of time)
c. Etoricoxib vs non-naproxen NSAIDs (includes studies with diclofenac as well as ibuprofen)

There are advantages and disadvantages to each comparison. The strength of the placebo comparison is that it provides insight as to the increase in events above the background rate. The limitations are the relatively short duration of exposure (at most 3 months) and the limited number of events. On the other hand, comparisons to naproxen or the non-naproxen NSAIDs suffer from the lack of a placebo group, making it difficult to dissect out whether the difference in rates of events is due to an increase in event rate in one group or a decrease in the other.

In addition, the following events will be presented:
a. Investigator reported events
b. Confirmed events (events that were investigator reported and adjudicated by a blinded committee)
c. APTC events

The events subsumed under the designation of confirmed and APTC events are provided in the following table:

Table :

Serious Adverse Events Included in the Thrombotic Cardiovascular Serious Adverse Experience and APTC Endpoints

Adjudication Committee Categories for Cardiovascular Events	Confirmed Thrombotic Cardiovascular Event	APTC Endpoint
Thrombotic Events		
Cardiac Events		
Acute MI	√	√
Fatal: Acute MI	√	√
Unstable Angina Pectoris	√	
Sudden and/or Unexplained Death	√	√
Resuscitated Cardiac Arrest	√	√
Cardiac Thrombus	√	
Peripheral Vascular Events		
Pulmonary Embolism	√	
Fatal: Pulmonary Embolism	√	
Peripheral Arterial Thrombosis	√	
Fatal: Peripheral Arterial Thrombosis	√	√
Peripheral Venous Thrombosis	√	
Cerebrovascular Events		
Ischemic Cerebrovascular Stroke	√	√
Fatal: Ischemic Cerebrovascular Stroke	√	√
Cerebrovascular Venous Thrombosis	√	
Fatal: Cerebrovascular Venous Thrombosis	√	√
Transient Ischemic Attack	√	
Hemorrhagic Events		
Hemorrhagic Cerebrovascular Stroke[1]		√
Fatal: Hemorrhagic Cerebrovascular Stroke[1]		√
Fatal: Hemorrhagic deaths of any cause		√

[1] These events are included as investigator-reported events but not confirmed thrombotic events.
APTC = Antiplatelet Trialists' Collaboration.

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II. Exposure

a. NDA: the following figure outlines the study design for the chronic studies for which the safety data is presented:

Overview of Study Designs: Chronic Exposure (Phase II/III) Studies

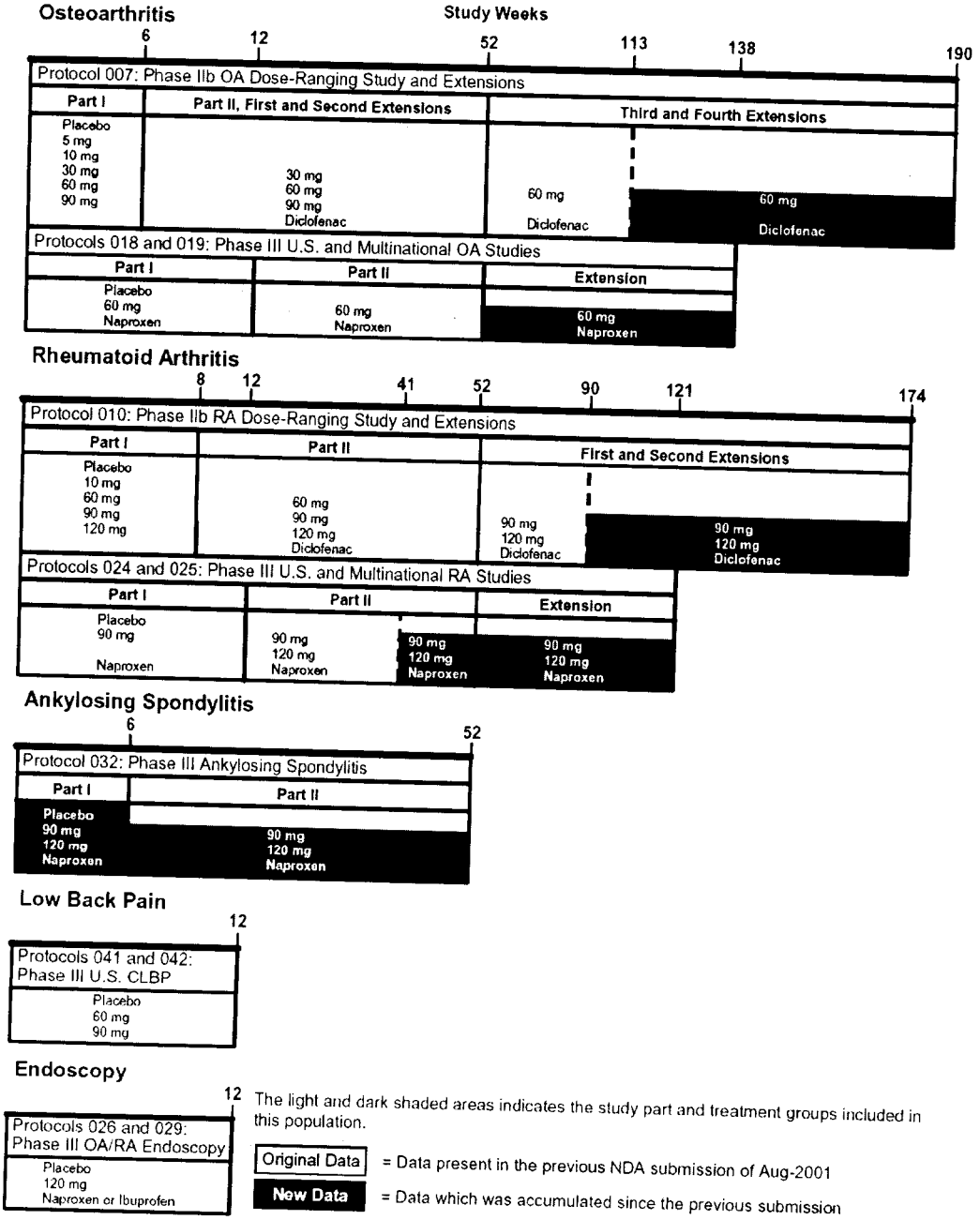

Table : Chronic exposure to etoricoxib across the NDA: number of patients on drug by dose and actual duration of treatment

Dose of etoricoxib	Total number of patients	Mean number of days on drug
Any dose	3649	407
<60 mg	535	145
60	1193	390
90	1736	361
120	1052	314
>120	35	5.4

b. EDGE study

This was a randomized, double-blind, multicenter study to evaluate the tolerability and effectiveness of etoricoxib 90 mg versus diclofenac sodium 150 mg in approximately 7000 subjects with osteoarthritis of the knee, hip, hand, or spine. Osteoarthritis was diagnosed with standard clinical criteria. Patients who required chronic treatment with a Nonsteroidal Antiinflammatory drug (NSAID) or cyclooxygenase (COX)-2 selective inhibitor were included. Patients who fulfilled entry criteria were instructed to discontinue their current OA therapy regimen for a 2- to 10-day washout period. Prior to randomization, patients who required low-dose aspirin for cardioprophylaxis (75 to 100 mg per day) during the study were identified as low-dose aspirin users and stratified accordingly. Eligible patients were randomized (in a 1:1 ratio) to either etoricoxib 90 mg or diclofenac 150 mg daily. Clinical safety and efficacy data were collected during clinic visits at screening baseline/randomization; 1, 4, 8, and 12 months of therapy, and at the End-of-Study visit. The primary endpoint was determined by the number of discontinuations due to clinical and laboratory GI adverse experiences. The use of ASA and gastroprotective agents was permitted in this study.

Table :

Duration of study therapy

	Etoricxoib 90 mg (N=3593)	Diclofenac 150 mg (N=3518)	Total (N=7111)
Duration of study therapy (months)			
Mean	9.3	8.9	9.1
SD	4.4	4.5	4.5
Median	11.5	11.3	11.4
Range	0.5 to 16.5	0.5 to 16.6	0.5 to 16.6
Total patient years	2789	2604	5393

III. Mortality

a. NDA

In the submission of the NDA (December 2003), a total of twenty-eight patients died in the etoricoxib development program, either while taking study medication, within 14 days of discontinuing study medication, or as a result of a serious adverse experience which began within 14 days of discontinuing study drug.

One additional death was reported (AN 10487, etoricoxib 120 mg, cardiac arrest), which occurred 21 days following discontinuation of study medication, and so is not included in the following analyses. All deaths occurred in Phase II/III Chronic Exposure Studies (OA, RA, AS, CLBP); none occurred in Phase I/Clinical Pharmacology, Acute Analgesia, or Acute Gouty Arthritis studies.

Table :

Summary of Deaths From Etoricoxib Studies

	Placebo PYR=335	Etoricoxib PYR=4103	Non-Naproxen PYR=501	Naproxen PYR=1728
	Counts Rates per 100 PYR (95% CI)			
Total Death*	**1** **0.30 (0.01, 1.66)**	**20** **0.49 (0.30, 0.75)**	**2** **0.40 (0.05, 1.44)**	**5** **0.29 (0.09, 0.68)**
CV Deaths	0 0.00 (0.00, 1.10)	10 0.24 (0.12, 0.45)	2 0.40 (0.05, 1.44)	3 0.17 (0.04, 0.51)
Thrombotic CV Deaths†	0 0.00 (0.00, 1.10)	9 0.22 (0.10, 0.42)	2 0.40 (0.05, 1.44)	2 0.12 (0.01, 0.42)
Non-CV Deaths	1 0.30 (0.01, 1.66)	10 0.24 (0.12, 0.45)	0 0.00 (0.00, 0.74)	2 0.12 (0.01, 0.42)

* Total Deaths includes CV Deaths + Non-CV Deaths.

† Thrombotic CV Deaths is a subset of CV Deaths, which excludes non-thrombotic CV deaths (AN 12201 [etoricoxib 120 mg, Protocol 026] and AN 9348 [naproxen, Protocol 024]).

Patient-years (PYR) at risk were obtained from updated summary tables of APTC endpoint. Combined etoricoxib patient-year exposure was obtained by adding the etoricoxib exposure in naproxen and non-naproxen NSAIDs controlled data, plus etoricoxib exposure from Protocols 041 and 042 (which were only placebo-controlled studies).

The event date for AN 10487 (etoricoxib 120 mg, Protocol 032) was beyond 14 days from the last therapy day and, thus, excluded in the above summary.

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Reviewers comments: While the rates appear to be similar in each group it is important to note that non-naproxen comparator cases are both related to the use of diclofenac. There were no cases reported associated with ibuprofen use. Diclofenac appears to have Cox-2 selectivity (See Figure below from NEJM article).

Figure :

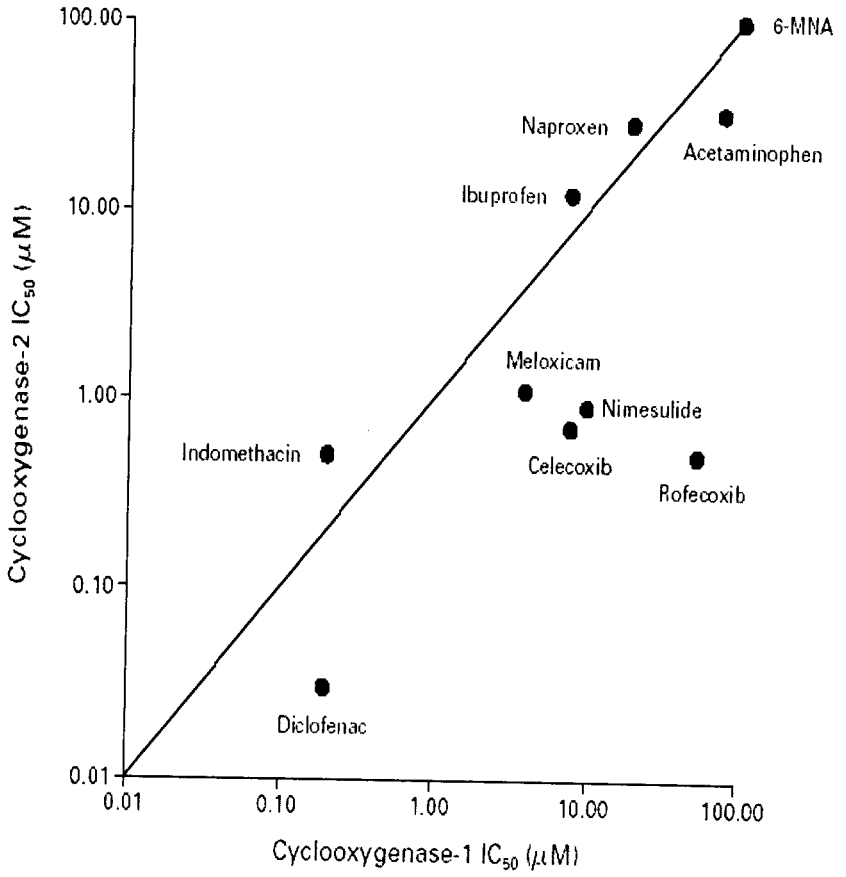


Figure 2. Concentrations of Various Drugs Required to Inhibit the Activity of Cyclooxygenase-1 and Cyclooxygenase-2 by 50 Percent (IC_{50}) in Assays of Whole Blood.

Each point is the mean of three or four values.[23-26] Drugs plotted below the diagonal line indicating equivalence are more potent inhibitors of cyclooxygenase-2 than drugs plotted on or above the line. 6-MNA denotes 6-methoxy-2-naphthylacetic acid.

It should also be noted that of those deaths considered to be CV/TE related, the time to death for etoricoxib had some of the shortest times listed (for example19, 97, 38 days compared to the CV/TE related deaths on diclofenac in which the 2 deaths were on days

1178 and 1204). However, there were other deaths in the etoricoxib group that occurred at later times such as days 687, 831, 225, 586, (but not as long a time as diclofenac).

There were 9 CV/TE events in etoricoxib (4103 patient years) vs 0 in placebo (335 patient years), 2 in naproxen (1727 patient years) and 2 in non-naproxen (501 patient years). The rates of events in etoricoxib vs naproxen is still about 1.9 fold greater. In non-naproxen NSAIDs rates of events based on patient years would indicate that non-naproxen is higher than etoricoxib, but again it must be emphasized that both events occurred at greater than 3 years.

Finally, it should be observed that the overall mortality rate in the naproxen group (0.29) is comparable to placebo (0.30). Furthermore, the mortality rate for etoricoxib is the highest (0.49) with the non-naproxen NSAIDs in the middle (0.40). The non-naproxen NSAIDS are composed mainly of diclofenac exposure, which as stated earlier appears to have some Cox-2 selectivity.

b. Deaths in the EGDE study

Overall, 14 deaths occurred in patients while on study therapy or within 14 days of discontinuation of study therapy: 8 in the etoricoxib group, and 6 in the diclofenac group (Table). In addition, 5 patients died during the off study drug period >14 days to the End-of-Study Visit: 2 in the etoricoxib group, and 3 in the diclofenac group. For additional comments about CV/TE events also see the section on CV events, below.

Reviewers comments: Based on adjudication, there were 3 CV/TE events in the etoricoxib group vs 1 in the diclofenac group (with the additional cases (>14 days) the total number of CV/TE cases is 3 in each treatment group).

Deaths in EDGE study

	Etoricoxib	Diclofenac
	3590 patient-years	3510 patient-years
Total deaths	8	6
CV deaths	4	3
Thrombotic CV deaths	3	1
Non-CV deaths	4	3

IV. CV

The sponsor examined the occurrence of CV thromboembolic events in 3 data sets including a comparison to placebo, to non-naproxen non-steroidals (diclofenac and ibuprofen), and to naproxen. The studies included in the placebo controlled data set are shown schematically below (naproxen and non-naproxen data sets are not shown). These data sets will be referred to in subsequent analyses. It should be noted that these data sets combine results from disparate studies across the NDA, including various indications (OA, RA, AS, CLBP etc), as well as various times of exposure etc. Additional sensitivity analyses will also be provided.

Thrombotic Cardiovascular Serious Adverse Experience Analysis
Placebo-Controlled Data Set

Osteoarthritis

Study Weeks: 6, 12, 52, 138, 190

Protocol 007: Phase IIb OA Dose-Ranging Study and Extensions

Part I	Part II, First and Second Extensions	Third and Fourth Extensions
Placebo 5 mg 10 mg 30 mg 60 mg 90 mg	30 mg 60 mg 90 mg Diclofenac	60 mg Diclofenac

Protocols 018 and 019: Phase III U.S. and Multinational OA Studies

Part I	Part II	Extension
Placebo 60 mg Naproxen	60 mg Naproxen	60 mg Naproxen

Rheumatoid Arthritis

8, 12, 52, 121, 174

Protocol 010: Phase IIb RA Dose-Ranging Study and Extensions

Part I	Part II	First and Second Extensions
Placebo 10 mg 60 mg 90 mg 120 mg	60 mg 90 mg 120 mg Diclofenac	90 mg 120 mg Diclofenac

Protocols 024 and 025: Phase III U.S. and Multinational RA Studies

Part I	Part II	Extension
Placebo 90 mg Naproxen	90 mg 120 mg Naproxen	90 mg 120 mg Naproxen

Ankylosing Spondylitis

6, 52

Protocol 032: Phase III Ankylosing Spondylitis

Part I	Part II
Placebo 90 mg 120 mg Naproxen	90 mg 120 mg Naproxen

Low Back Pain

12

Protocols 041 and 042: Phase III U.S. CLBP

Placebo
60 mg
90 mg

Endoscopy

12

Protocols 026 and 029: Phase III OA/RA Endoscopy

Placebo
120 mg
Naproxen or Ibuprofen

The light and dark shaded areas indicates the study part and treatment groups included in this population.

Original Data = Data present in the previous NDA submission of Aug-2001

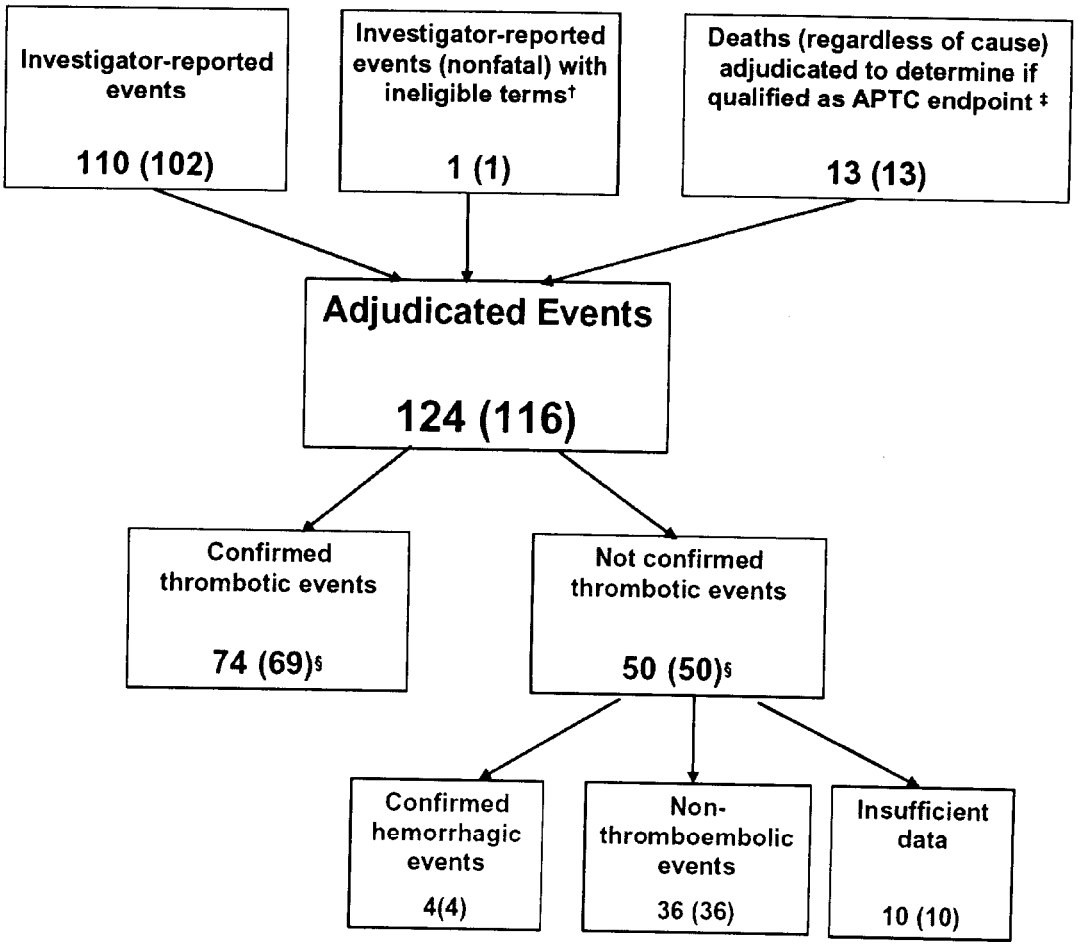
New Data = Data which was accumulated since the previous submission

Adjudication and analysis of CV/TE events across the chronic studies in the NDA:

Investigator reported events that are eligible for adjudication, as well as all deaths, were sent blinded to an adjudication committee after review by a Merck medical monitor.

Figure :

Accounting of Events (Patients)



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‡ Adjudicated at the sponsor's request (neurological disorder).

† All deaths in this category were reported with terms *ineligible* for adjudication, but were adjudicated to determine if they qualified as APTC endpoints. The remaining 16 deaths in the etoricoxib program had terms eligible for adjudication and thus are included under "Investigator-Reported Events".

§ Three patients had both confirmed and not confirmed thrombotic events.

Table :

Cardiovascular Events Adjudicated As Not -Confirmed Thrombotic Events, Protocols (007, 010, 018, 019, 024, 015, 026, 019, 032, 041, 042, and 805)

	Placebo PY=300		Etoricoxib PY=3930		Naproxen PY=1497		Diclofenac PY=425	
	n	Rate/ 100 PY	n	Rate/ 100 PY	n	Rate/ 100 PY	n	Rate/ 100 PY
Not Confirmed Thrombotic Events	**3**	**1.0**	**39**	**1.0**	**7**	**0.5**	**1**	**0.2**
Confirmed Hemorrhagic	0	0	3	0.1	1	0.1	0	0
Non-thromboembolic	3	1.0	27	0.7	5	0.3	1	0.2
Insufficient Data	0	0	9	0.2	1	0.1	0	0
PY=Patient-Years								

Reviewers comments: of note, there are 9 events in the etoricoixb group that had "insufficient" information vs only 1 in the naproxen group. If we apply the percent of cases that were adjudicated as CV/TE (74/124, see above figure) to these numbers, there are potentially 5 additional cases in the etoricoxib group. There is also a greater rate of cases "not confirmed thrombotic" in the etoricoxib group(1.0) vs other groups (0.2-0.5) vs a similar rate in the placebo group (1.0). These potential cases should be considered in subsequent analyses.

The sponsor provided the table below that summarizes the overall results of both confirmed as well as APTC events. It should be noted that the placebo comparison includes 6 and 8 week trials as well as AS and CLBP subjects.

Table:

Absolute Rate and Relative Risk (and Associated 95% CI)
Thrombotic Cardiovascular Serious Adverse Experiences and APTC Endpoint

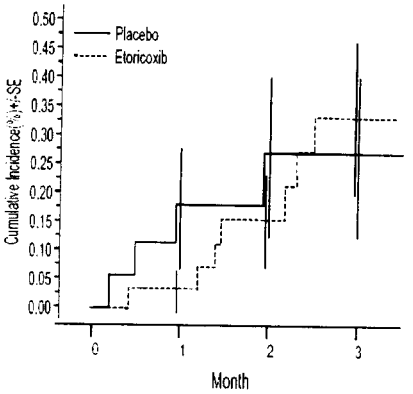
Comparisons	N	Cases/PYR*	Rate‡ (95% CI)	Relative Risk§ (95% CI)
Thrombotic Cardiovascular Serious Adverse Experiences				
Etoricoxib	2818	7/560	1.25 (0.50, 2.58)	1.11 (0.32, 3.81)
Placebo	1767	4/335	1.19 (0.33, 3.06)	--
Etoricoxib	1266	12/1522	0.79 (0.41, 1.38)	0.83 (0.26, 2.64)
Non-Naproxen NSAIDs	718	4/501	0.80 (0.22, 2.04)	--
Etoricoxib	1960	34/2480	1.37 (0.95, 1.92)	1.70 (0.91, 3.18)
Naproxen 1000 mg	1497	14/1727	0.81 (0.44, 1.36)	--
APTC Endpoint				
Etoricoxib	2818	6/560	1.07 (0.39, 2.33)	1.80 (0.32, 18.19)
Placebo	1767	2/335	0.60 (0.07, 2.16)	--
Etoricoxib	1266	10/1524	0.66 (0.31, 1.21)	0.87 (0.24, 3.24)
Non-Naproxen NSAIDs	718	3/501	0.60 (0.12, 1.75)	--
Etoricoxib	1960	27/2481	1.09 (0.72, 1.58)	2.72 (1.18, 6.27)
Naproxen 1000 mg	1497	7/1728	0.41 (0.16, 0.83)	--

* Patient-years at risk.
‡ Per 100 PYR.
§ Relative risk using Cox model stratified by therapeutic block where the number of cases is at least 11, otherwise relative risk is ratio of rates.
APTC = Antiplatelet Trialists' Collaboration; CI = Confidence interval; PYR = Patient-years at risk.

[504]

Kaplan-Meier Estimates of Cumulative Incidence for Confirmed Thrombotic Cardiovascular Serious Adverse Experiences

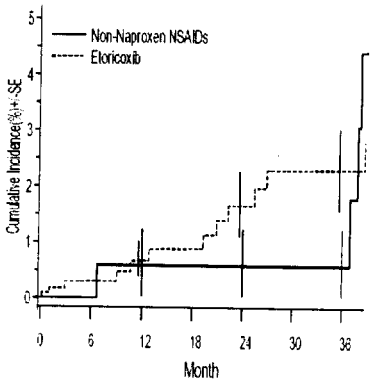
Placebo-Controlled Data Set*



‡ Patients at Risk

Placebo	1767	1435	1074	507
Etoricoxib	2818	2625	1710	801

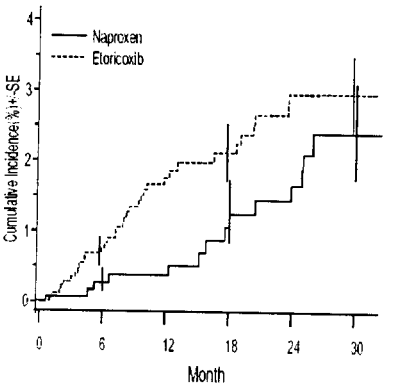
Non-Naproxen NSAIDs Controlled Data Set‡



‡ Patients at Risk

Non-Naproxen NSAIDs	718	174	133	116	94	86	83
Etoricoxib	1286	604	524	415	352	295	236

Naproxen-Controlled Data Set*



‡ Patients at Risk

Naproxen	1497	942	721	523	468	143
Etoricoxib	1960	1411	1124	749	668	145

* No events occurred after the last shown time axis.
‡ One event (in etoricoxib) occurred after the last shown time axis. All events are included in the analysis.
Error bars are ± SE of cumulative incidence (%) at the indicated time points.
Plots were truncated when the risk size in any arm is < 50.
TCVSAE = Confirmed Thrombotic Cardiovascular Serious Adverse Experiences.

Reviewers comments: Examination of the KM curves for each group comparison provides additional interesting information especially for the non-naproxen comparisons. As can be seen, 3 of the 4 events in the non-naproxen group occurred at greater than 3 years while all but one of the cases in the etoricoxib group occurred at less than 2 years

of exposure. It is not clear what the optimal time is to study this type of outcome, but since CV events are relatively frequent, the longer the period of study the more events that will accrue. Studies that are very long may make it difficult to identify any drug related effect. If there are any drug related CV effects, these would likely occur at a time point earlier than 3 years. Thus, inclusion of events at 3 years may not be appropriate.

A quote from sponsor is appropriate here: "As previously mentioned, these Kaplan-Meier analyses, while generally representative of the data from the chronic exposure studies, do have substantial limitations. Circumstances where these data can be considered to be potentially unreliable include: (1) low frequency events for which the number of patients per treatment group may be insufficient to detect meaningful differences (i.e., a small number of chance events could bias interpretation of results); (2) data points occurring after a substantial number of discontinuations has occurred in one or more treatment groups such that treatment groups are no longer balanced." "Because of issues of self-selection (a concern among patients who have entered study extensions) and the lack of power to detect events (due to patient dropouts) the reliability of data after 2 years is considered low."

Placebo analyses

The following analyses are presented for CV events pooled across all studies with a placebo control period.

The sponsor was requested to provide an analysis examining only the 12 week placebo controlled trials (without the 6 and 8 week data sets; the 6 and 8 week trials add patient years of exposure without any CV events, likely because they are very short in duration), and the results are provided below:

Table :

Absolute Rate and Relative Risk (and Associated 95% CI)
Thrombotic Cardiovascular Serious Adverse Experiences, APTC Endpoint, and Investigator-Reported Endpoint
12-week placebo-controlled data of studies in OA, RA, CLBP and surveillance endoscopy

Comparisons	N	Cases/PYR[†]	Rate[‡](95% CI)	Relative Risk[§] (95% CI)
TCVSAE Endpoint				
Etoricoxib	2019	6/453	1.32 (0.49, 2.88)	1.33 (0.28, 8.22)
Placebo	1491	3/302	0.99 (0.21, 2.91)	-
APTC Endpoint				
Etoricoxib	2019	5/453	1.10 (0.36, 2.57)	3.33 (0.37, 157.36)
Placebo	1491	1/302	0.33 (0.01, 1.85)	-
Investigator Reported Events				
Etoricoxib	2019	10/453	2.21 (1.06, 4.06)	1.33 (0.45, 3.93)
Placebo	1491	5/302	1.66 (0.54, 3.87)	-

[†] Patient-years at risk.
[‡] Per 100 patient-years.
[§] Relative risk using Cox model where the number of cases is at least 11: otherwise, relative risk is a ratio of rates.

Reviewers comments: this analysis is of investigator reported events and is slightly different than the original analysis shown previously which described "confirmed" events.

Table :

12-week placebo-controlled data of studies in OA, RA, CLBP and surveillance endoscopy

Summary of Patients with Confirmed Thrombotic Cardiovascular Serious Adverse Experiences by Class of Terms

Category	Etoricoxib (N=2019) 453 Patient Years		Placebo (N=1491) 302 Patient Years	
	n (%)[†]	Rate[‡]	n (%)[†]	Rate[‡]
Total number of patients with TCVSAE[*] Endpoint	**6 (0.30)**	**1.32**	**3 (0.20)**	**0.99**
Cardiac Events	3 (0.15)	0.66	0 (0.00)	0.00
Acute myocardial infarction	1 (0.05)	0.22	0 (0.00)	0.00
Unstable angina pectoris	1 (0.05)	0.22	0 (0.00)	0.00
Sudden/unknown cause of death	1 (0.05)	0.22	0 (0.00)	0.00
Peripheral Vascular Events	1 (0.05)	0.22	2 (0.13)	0.66
Pulmonary embolism	1 (0.05)	0.22	0 (0.00)	0.00
Peripheral venous thrombosis	0 (0.00)	0.00	2 (0.13)	0.66
Cerebrovascular Events	3 (0.15)	0.66	1 (0.07)	0.33
Ischemic cerebrovascular stroke	3 (0.15)	0.66	1 (0.07)	0.33

Note: Patient with multiple events may be counted more than once in different terms but only once in one term.

[*] TCVSAE = Confirmed Thrombotic Cardiovascular Serious Adverse Experience.

[†] Crude incident (n/Nx100)

[‡] Events per 100 patient-years

Reviewers comments: note that this analysis includes only those studies that contain a full 12 week placebo duration, hence, rates of CV events compared to placebo are slightly different from the original sponsor analysis, but again, do not favor etoricoxib. There are more cardiac and CNS events in the etoricoxib treatment group, but numbers of events are small.

The following table provides a more detailed analysis of events by treatment group:

Table:

Placebo-Controlled Data Set—Summary of Patients With Confirmed Thrombotic Cardiovascular Serious Adverse Experiences by Class of Terms

Endpoint Terms	Etoricoxib (N=2818) (PYR=560) n (%)[‡]	Etoricoxib (N=2818) (PYR=560) Rate[*]	Placebo (N=1767) (PYR=335) n (%)[‡]	Placebo (N=1767) (PYR=335) Rate[*]
Patients with One or More Thrombotic Cardiovascular Serious Adverse Experiences	**7 (0.25)**	**1.25**	**4 (0.23)**	**1.19**
Cardiac Events	4 (0.14)	0.71	0 (0.00)	0.00
Acute myocardial infarction	1 (0.04)	0.18	0 (0.00)	0.00
Fatal acute myocardial infarction	1 (0.04)	0.18	0 (0.00)	0.00
Unstable angina pectoris	1 (0.04)	0.18	0 (0.00)	0.00
Sudden/unknown cause of death	1 (0.04)	0.18	0 (0.00)	0.00
Peripheral Vascular Events	1 (0.04)	0.18	2 (0.11)	0.60
Pulmonary embolism	1 (0.04)	0.18	0 (0.00)	0.00
Peripheral venous thrombosis	0 (0.00)	0.00	2 (0.11)	0.60
Cerebrovascular Events	3 (0.11)	0.54	2 (0.11)	0.60
Ischemic cerebrovascular stroke	3 (0.11)	0.54	2 (0.11)	0.60

‡ Crude incident (n/Nx100).
* Events per 100 patient-years.
Note: Patient with multiple events may be counted more than once in different terms but only once in the "One or More" category.

[504]

Reviewers comments: Of note there are 4 cardiac events in etoricoxib treated subjects vs 0 in placebo. However, there are 2 DVTs in placebo vs 0 in etoricoxib. These are small numbers of events but the MI data is consistent with the data in other treatment group comparisons (see below). There is no difference in CNS events.

Non-naproxen analysis

Table :

Non-Naproxen-NSAID-Controlled Data Set—Summary of Patients With Confirmed Thrombotic Cardiovascular Serious Adverse Experiences by Class of Terms

Endpoint Terms	Etoricoxib (N=1266) (PYR=1522)		Non-Naproxen NSAIDs: Combined (N=718) (PYR=501)		Non-Naproxen NSAIDs: Diclofenac (N=492) (PYR=447)		Non-Naproxen NSAIDs: Ibuprofen (N=226) (PYR=54)	
	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]	n (%)[1]	Rate[2]
Patients with One or More Thrombotic Cardiovascular Serious Adverse Experiences	**12 (0.95)**	**0.79**	**4 (0.56)**	**0.80**	**4 (0.81)**	**0.89**	**0 (0.00)**	**0.00**
Cardiac Events	11 (0.87)	0.72	2 (0.28)	0.40	2 (0.41)	0.45	0 (0.00)	0.00
Acute myocardial infarction	3 (0.24)	0.20	0 (0.00)	0.00	0 (0.00)	0.00	0 (0.00)	0.00
Fatal acute myocardial infarction	2 (0.16)	0.13	1 (0.14)	0.20	1 (0.20)	0.22	0 (0.00)	0.00
Unstable angina pectoris	4 (0.32)	0.26	0 (0.00)	0.00	0 (0.00)	0.00	0 (0.00)	0.00
Sudden/unknown cause of death	2 (0.16)	0.13	1 (0.14)	0.20	1 (0.20)	0.22	0 (0.00)	0.00
Cerebrovascular Events	2 (0.16)	0.13	2 (0.28)	0.40	2 (0.41)	0.45	0 (0.00)	0.00
Ischemic cerebrovascular stroke	1 (0.08)	0.07	1 (0.14)	0.20	1 (0.20)	0.22	0 (0.00)	0.00
Transient ischemic attack	1 (0.08)	0.07	1 (0.14)	0.20	1 (0.20)	0.22	0 (0.00)	0.00

[1] Crude incident (n/Nx100).
[2] Events per 100 patient-years.
Note: Patient with multiple events may be counted more than once in different terms but only once in the "One or More" category.
TCVSAE = Confirmed Thrombotic Cardiovascular Serious Adverse Experiences.

[504]

Reviewers comments: Of note, there are 11 cardiac events in the etoricoxib group vs 2 in the non-naproxen combined group which is made up of diclofenac events only (there were no events in the ibuprofen treatment arm). Three of the 4 events in the non-naproxen group occurred at greater than 3 years of exposure (as noted in a review of the KM plots). All but one of the events in etoricoxib occurred within the first 2 years. There are also 5 MIs in the etoricxoib group vs 1 in the diclofenac group. Although there is no difference in the absolute numbers of CNS events the rates are higher in the diclofenac group because of the fewer patient-years of exposure. Numbers are small and firm conclusions are difficult.

Naproxen analysis

Table :

Naproxen-Controlled Data Set—Summary of Patients With Confirmed Thrombotic Cardiovascular Serious Adverse Experiences by Class of Terms

Endpoint Terms	Etoricoxib (N=1960) (PYR=2480)		Naproxen (N=1497) (PYR=1727)	
	n (%)*	Rate‡	n (%)*	Rate‡
Patients with One or More Thrombotic Cardiovascular Serious Adverse Experiences	**34 (1.73)**	**1.37**	**14 (0.94)**	**0.81**
Cardiac Events	21 (1.07)	0.85	9 (0.60)	0.52
Acute myocardial infarction	10 (0.51)	0.40	5 (0.33)	0.29
Fatal acute myocardial infarction	2 (0.10)	0.08	1 (0.07)	0.06
Unstable angina pectoris	6 (0.31)	0.24	3 (0.20)	0.17
Sudden/unknown cause of death	3 (0.15)	0.12	0 (0.00)	0.00
Peripheral Vascular Events	2 (0.10)	0.08	5 (0.33)	0.29
Pulmonary embolism	2 (0.10)	0.08	2 (0.13)	0.12
Peripheral arterial thrombosis	0 (0.00)	0.00	1 (0.07)	0.06
Peripheral venous thrombosis	0 (0.00)	0.00	2 (0.13)	0.12
Cerebrovascular Events	12 (0.61)	0.48	2 (0.13)	0.12
Ischemic cerebrovascular stroke	10 (0.51)	0.40	0 (0.00)	0.00
Fatal ischemic cerebrovascular stroke	0 (0.00)	0.00	1 (0.07)	0.06
Transient ischemic attack	2 (0.10)	0.08	1 (0.07)	0.06

* Crude incident (n/Nx100).
‡ Events per 100 patient-years.
Note: Patient with multiple events may be counted more than once in different terms but only once in the "One or More" category.

[504]

Reviewers comments: Both cardiac and cerebrovascular events are higher in the etoricoxib group. Whether naproxen is protective has not been demonstrated.

Additional analyses:

Table: Investigator reported event rates for combined studies

Comparisons	N	Cases/PYR[†]	Rate[‡](95% CI)	Relative Risk[§] (95% CI)
Investigator Reported Cardiovascular events				
Etoricoxib	2818	13/560	2.32 (1.24, 3.97)	1.34 (0.50, 3.54)
Placebo	1767	6/335	1.79 (0.66, 3.90)	-
Etoricoxib	1266	23/1522	1.51 (0.96, 2.27)	1.46 (0.54, 3.89)
Non-Naproxen NSAIDs	718	5/501	1.00 (0.32, 2.33)	-
Etoricoxib	1960	48/2473	1.94 (1.43, 2.57)	1.90 (1.10, 3.27)
Naproxen 1000 mg	1497	18/1725	1.04 (0.62, 1.65)	-

[†] Patient-years at risk.

[‡] Per 100 PYR.

[§] Relative risk using Cox model where the number of cases is at least 11; otherwise, relative risk is a ratio of rates.

Reviewers comments: Instead of relying on the Merck appointed adjudication committee, another way to look at the CV events is to analyze the results using investigator reported events. Overall, etoricoxib appears worse than naproxen. For the placebo period, etoricoxib appears worse than placebo for CV/TE events.

An additional endpoint "new ischemic heart disease events" was requested and provided by the sponsor (see below). As requested by the Review Division in the context of the Mar-2003 preNDA meeting, data are presented using an endpoint which is defined with the purpose of identifying patients with no previous history of ischemic heart disease who had an event consistent with ischemic heart disease. This endpoint, which will be termed 'New Ischemic Heart Disease,' is defined post hoc as the composite of any patient with one of the following
events who has no documented history of ischemic heart disease:

- Confirmed thrombotic serious adverse experiences which represent a cardiac event
- Nonserious cardiovascular broader terms of angina pectoris, ischemic heart disease, myocardial infarction, or ST-T change compatible with ischemia

In order to qualify as an event for this endpoint, a patient was required to both have incurred one of these events as well as have no documented previous history of ischemic heart disease (defined as no medical history of any of the following broader terms: ST segment depression, ST segment elevation, ST-T change compatible with ischemia, acute

myocardial infarction, age indeterminate myocardial infarction, angina pectoris, angioplasty, atherosclerosis, cardiac arrest, coronary angioplasty, coronary artery disease, coronary artery stenosis, coronary artery stent placement, coronary bypass, coronary vascular surgery, ischemic heart disease, myocardial infarction, myocardial infarction complication, or unstable angina).

Table:

Summary Statistics for New Ischemic Heart Disease

Treatment	Number of Events	Total Number of Patients	Patient-Years	Rate per 100 Patient-Years	
				%	95% CI
Placebo-Controlled Population					
Etoricoxib	4	2689	535	0.75	(0.20, 1.91)
Placebo	1	1678	319	0.31	(0.01, 1.75)
Non-Naproxen-Controlled Population					
Etoricoxib	12	1197	1480	0.81	(0.42, 1.42)
Non-Naproxen NSAIDs	2	672	488	0.41	(0.05, 1.48)
Naproxen-Controlled Population					
Etoricoxib	22	1870	2382	0.92	(0.58, 1.40)
Naproxen	10	1423	1644	0.61	(0.29, 1.12)

[1] Patient-years at risk.
[2] Per 100 patient-years.

[507]

Reviewers comments: Of note, cases of "new onset ischemic heart disease" are greater in the etoricxoib group compared to all comparators including placebo.

Additional subgroup analyses were performed by the sponsor and are presented below.

Table :

Rates of TCV SAE events tabulated by etoricoxib indication, placebo controlled data set

	etoricoxib		placebo	
	N	Cases/pyr	N	Cases/pyr
RA	1240	5/243	990	2/176
OA	958	1/197	465	2/102
other	620	1/120	57	0/57
combined	2818	7/560	1767	4/335

Reviewers comments: It is interesting to note that 5/7 CV events in etoricoxib treated subjects occurred in the RA subgroup (while events in the placebo group are evenly divided between the RA and OA studies).

Table :

Summary of CV Events and Rates (95% CI) in Placebo, 60-, 90-, & 120-mg Etoricoxib, Naproxen, and Ibuprofen Groups During the Placebo-Controlled Period

Treatment	N	Cases[†] / PYR[‡]	Rates per 100 PYR (95% CI)
Thrombotic Cardiovascular Serious Adverse Experiences			
Placebo	1767	4/335	1.19 (0.33, 3.06)
Etoricoxib 60 mg	896	1/182	0.55 (0.01, 3.06)
Etoricoxib 90 mg	1238	6/233	2.57 (0.94, 5.60)
Etoricoxib 120 mg	684	0/145	0.00 (0.00, 2.55)
Naproxen	1133	0/232	0.00 (0.00, 1.59)
Ibuprofen	226	0/54	0.00 (0.00, 6.83)
APTC Endpoint			
Placebo	1767	2/335	0.60 (0.07, 2.16)
Etoricoxib 60 mg	896	1/182	0.55 (0.01, 3.06)
Etoricoxib 90 mg	1238	4/233	1.71 (0.47, 4.39)
Etoricoxib 120 mg	684	1/145	0.69 (0.02, 3.85)
Naproxen	1133	0/232	0.00 (0.00, 1.59)
Ibuprofen	226	0/54	0.00 (0.00, 6.83)
Investigator-reported Events			
Placebo	1767	6/335	1.79 (0.66, 3.90)
Etoricoxib 60 mg	896	3/182	1.65 (0.34, 4.82)
Etoricoxib 90 mg	1238	9/233	3.86 (1.77, 7.33)
Etoricoxib 120 mg	684	1/145	0.69 (0.02, 3.86)
Naproxen	1133	0/232	0.00 (0.00, 1.59)
Ibuprofen	226	0/54	0.00 (0.00, 6.83)

[†] Number of patients with events
[‡] Patient-years at risk.
APTC = Antiplatelet Trialists' Collaboration

Reviewers comments: Although there are few events in total, this analysis demonstrates that the 90 mg dose appears to drive the increase in CV events in the placebo period, while the 60 mg dose appears to be more similar to placebo.

An additional analysis looking at the first 3 month period of the EDGE trial is provided below (even though the EDGE trial did not have a placebo period).

Table : EDGE study

Analysis of Thrombotic Cardiovascular Serious Adverse Experiences, APTC Endpoint and Investigator Reported Events
(Events within 14 Days after Study Therapy Discontinuation)
3 Months Follow Up

Comparisons	N	Cases/PYR[†]	Rate[‡] (95% CI)
Thrombotic Cardiovascular Serious Adverse Experiences			
Etoricoxib 90 mg	3593	12/831	1.44 (0.75, 2.52)
Diclofenac Sodium 150 mg	3518	7/805	0.87 (0.35, 1.79)
APTC Endpoint			
Etoricoxib 90 mg	3593	8/831	0.96 (0.42, 1.90)
Diclofenac Sodium 150 mg	3518	7/805	0.87 (0.35, 1.79)
Investigator Reported			
Etoricoxib 90 mg	3593	13/831	1.57 (0.83, 2.68)
Diclofenac Sodium 150 mg	3518	13/805	1.62 (0.86, 2.76)

[†] Patient-years at risk.
[‡] Per 100 PYR.
APTC = Antiplatelet Trialists' Collaboration; CI = Confidence interval; PYR = Patient-years at risk.

Reviewers comments: This is an analysis of the first 3 months of the EDGE study that was provided by the sponsor so as to provide the same time of exposure as the placebo period in the NDA. As can be seen there appears to be an increase in events in the etoricoxib group at least for the adjudicated/confirmed analysis (although the other analyses do not support this).

Analyses by aspirin use are provided by the sponsor for the naproxen group comparisons only because there are few exposures in the other treatment groups.

Table :

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
Subgroup Analysis by Aspirin Use
Etoricoxib Versus Naproxen

Subgroup	Treatment	n/N (%)	Patient-Years	Rate* (95% CI†)
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences				
Total Cohort	Etoricoxib	34/1960 (1.73)	2480	1.37 (0.95, 1.92)
	Naproxen	14/1497 (0.94)	1727	0.81 (0.44, 1.36)
Aspirin User	Etoricoxib	3/111 (2.70)	156	1.92 (0.40, 5.61)
	Naproxen	2/84 (2.38)	110	1.82 (0.22, 6.56)
Not Aspirin User	Etoricoxib	31/1849 (1.68)	2323	1.33 (0.91, 1.89)
	Naproxen	12/1413 (0.85)	1617	0.74 (0.38, 1.30)

* Number of events per 100 patient-years.
† If no events within the treatment group, the CI is a one-sided 97.5% CI.
n/N=the number of patients with events/total number of patients; CI=Confidence Interval.

Reviewers comments: Interestingly, there is little difference in CV events between etoricoxib and naproxen for the ASA users group. This is of importance because the EDGE study (see below) enrolled about 30% ASA users. At the time it was felt that this was a high risk population for CV events and thus should be closely examined. Although rates of events are higher in the ASA users group, there is no difference between the treatment groups suggesting that ASA use may obscure any effect of etoricoxib on the propensity to develop CV events. This has implication for the EGDE study since it was designed to show non-inferiority of etoricoxib to diclofenac (see EDGE study below).

EDGE data for CV/TE events

The results of the EDGE study are presented below.

A few comments about this study are appropriate here.

First, the study only compared etoricoxib to diclofenac. Diclofenac is a non-naproxen NSAID which, however, has some Cox-2 selectivity. Although the Division recommended that the sponsor include at least one additional comparator, this was not done. Thus, comparisons between etoricoxib and diclofenac may not entirely resolve the issue of CV safety.

Second, this study only recruited subjects with OA, and RA patients were not studied. There is a significant body of data that suggests that RA itself is a cardiac risk factor.

Third, the dose studied was etoricoxib 90 mg which although the highest labeled chronic dose is not the highest dose at which etoricoxib will ultimately be labeled at (which is 120 mg for acute pain). There is no data provided in the NDA to actually compare (interms of efficacy), etoricoxib and diclofenac during a placebo controlled period. In this study, the 90 mg dose is compared to the maximal doses of diclofenac. Thus, we do not know if 90 mg etoricoxib is comparable to 150 mg diclofenac (in terms of efficacy, which could have implications on the safety analysis). However, there was no dose response noted in the NDA for CV safety issues so that 90 and 120 mg may not be that much different in terms of CV risk (although there is little data to support this concept).

Fourth, subjects in this study could have been on previous Cox-2 agents. Potentially this may eliminate some high risk individuals especially if they tolerated the previous Cox-2 agent.

Fifth, there was a large number of subjects on ASA therapy. Although this group is likely a high risk population, and one that should be studied, the use of ASA may also potentially obscure any differences between groups, especially if ASA is protective of CV events (and protective even if use of etoricoxib leads to an increase in the rate of CV events). This hypothesis is supported by the fact that in an analysis of the NDA data set, the difference in CV event rates was lost in the naproxen vs etoricoxib comparison for those subjects on ASA. Thus the use of ASA in addition to the above discussed issues could easily confound the results of any CV analysis. It is also interesting to note that in the NDA data base the average ASA use varied from a few percent of subjects up to about 20% with most instances below 10% use, while in the EDGE study there was approximately 28% ASA use.

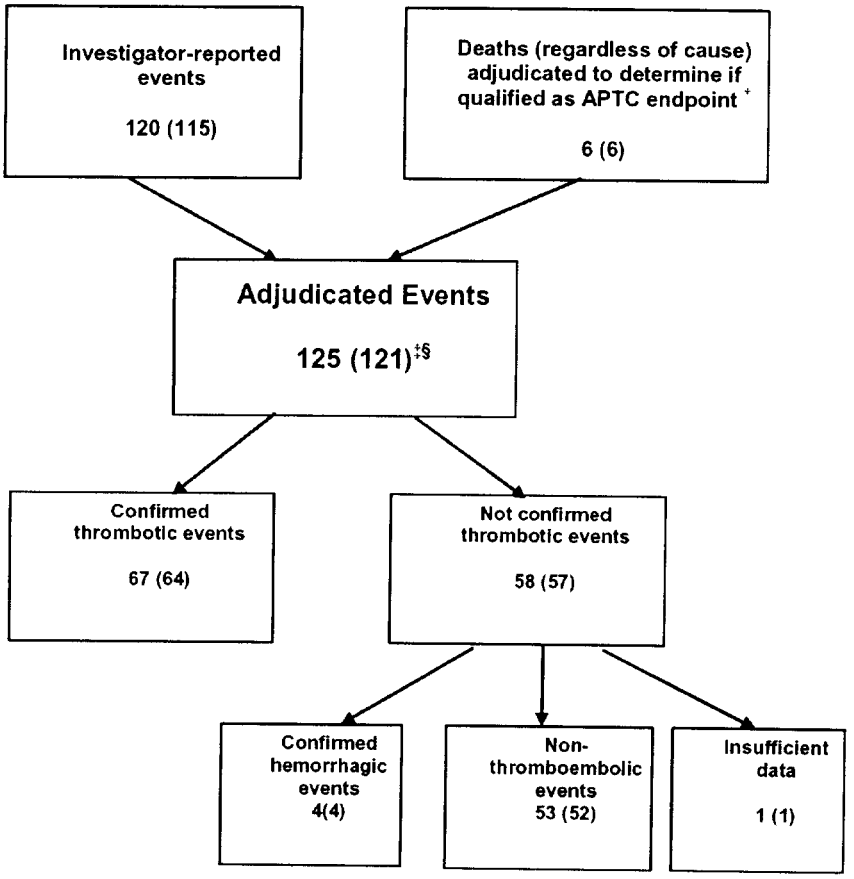
Sixth, a review of the number of subjects with either >2 CV risk factors or ASA indicated, reveals about 2600 subjects (out of the 7000 total subjects) who are at high risk for CV events. This could potentially lead to an increase in the background rate of events, further making differences between the groups difficult to detect. Taken together, the factors discussed may obscure differences between etoricoxib and diclofenac and make firm conclusions as to the true effects of etoricoxib on CV safety difficult.

Based on the above discussion, subgroup analyses will be important to dissect out the effect of these factors on the rate of CV events.

The next figure shows an accounting of the subjects referred for adjudication of cardiac events.

Figure:

Accounting of Events (Patients)
Events Within 14 Days After Study Therapy Discontinuation



+ All deaths in this category were reported with terms ineligible for adjudication, but were adjudicated to determine if they qualified as APTC endpoints. The remaining 12 deaths in this study had eligible terms for adjudication and thus included under "Investigator-Reported Events." One death occurred >28 days after study therapy discontinuation and was not eligible for adjudication.

‡ One event (AN 31092) was pending adjudication at the time of this analysis but included under "Investigator-Reported Events."

§ One patient (AN 27574) was included in both the "Investigator-Reported Event" and as a "Death."

Data Source: [4.35]

Table :

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
Relative Risk and Associated 95% CI

Treatment	N	n/PYR*	Rate‡(95% CI)	Relative Risk (95% CI)
Events within 14 days after study therapy discontinuation				
Etoricoxib 90 mg	3593	34 / 2789	1.22 (0.84 , 1.70)	1.04 (0.63 , 1.69)
Diclofenac Sodium 150 mg	3518	30 / 2607	1.15 (0.78 , 1.64)	
Events within 28 days after study therapy discontinuation				
Etoricoxib 90 mg	3593	37 / 2926	1.26 (0.89 , 1.74)	0.99 (0.62 , 1.59)
Diclofenac Sodium 150 mg	3518	34 / 2740	1.24 (0.86 , 1.73)	
All events (regardless of time)				
Etoricoxib 90 mg	3593	40 / 2927	1.37 (0.98 , 1.86)	0.99 (0.63 , 1.55)
Diclofenac Sodium 150 mg	3518	37 / 2742	1.35 (0.95 , 1.86)	

* Patient-years at risk;
‡ Per 100 PYR

Reviewers comments: An overall analysis of CV events demonstrates no difference between the groups.

Table :

Summary of Confirmed Thrombotic Cardiovascular Serious Adverse Events
by Class of Terms
(Events within 14 Days after Study Therapy Discontinuation)

Confirmed Adjudicated Event	Etoricoxib 90 mg (N=3593) 2789 Patient-Years			Diclofenac Sodium 150 mg (N=3518) 2607 Patient-Years		
	n(%)[†]	Rate[‡]	95% CI	n(%)[†]	Rate[‡]	95% CI
Total number of patients with Endpoint	34 (0.95)	1.22	(0.84 , 1.70)	30 (0.85)	1.15	(0.78 , 1.64)
Cardiac Events	26 (0.72)	0.93	(0.61 , 1.37)	19 (0.54)	0.73	(0.44 , 1.14)
Acute myocardial infarction	18 (0.50)	0.65	(0.38 , 1.02)	11 (0.31)	0.42	(0.21 , 0.76)
Sudden cardiac death	2 (0.06)	0.07	(0.01 , 0.26)	1 (0.03)	0.04	(0.00 , 0.21)
Unstable angina pectoris	6 (0.17)	0.22	(0.08 , 0.47)	7 (0.20)	0.27	(0.11 , 0.55)
Cerebrovascular Events	7 (0.19)	0.25	(0.10 , 0.52)	7 (0.20)	0.27	(0.11 , 0.55)
Fatal ischemic cerebrovascular stroke	1 (0.03)	0.04	(0.00 , 0.20)	0 (0.00)	0.00	---
Ischemic cerebrovascular stroke	3 (0.08)	0.11	(0.02 , 0.31)	6 (0.17)	0.23	(0.08 , 0.50)
Transient ischemic attack	3 (0.08)	0.11	(0.02 , 0.31)	2 (0.06)	0.08	(0.01 , 0.28)
Peripheral Vascular Events	3 (0.08)	0.11	(0.02 , 0.31)	4 (0.11)	0.15	(0.04 , 0.39)
Peripheral arterial thrombosis	0 (0.00)	0.00	---	1 (0.03)	0.04	(0.00 , 0.21)
Peripheral venous thrombosis	2 (0.06)	0.07	(0.01 , 0.26)	0 (0.00)	0.00	---
Pulmonary embolism	1 (0.03)	0.04	(0.00 , 0.20)	3 (0.09)	0.12	(0.02 , 0.34)

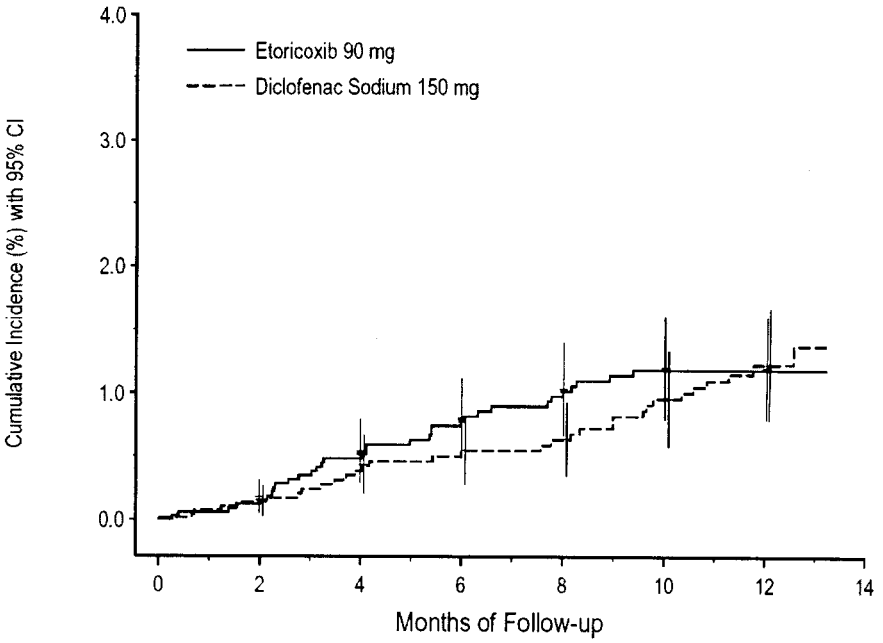
Note: patients with multiple events may be counted more than once in different terms, but only once in each term
[†]: Crude Incidence (n/N×100)
[‡]: Events per 100 Patient-Years

Reviewers comments: This table presents one of the subset analyses that are important to understand the results of the EDGE study. When the overall numbers of CV/TE events are examined there is no difference between the treatment groups, a closer examination reveals that there is an increase in overall cardiac events (26 vs 19) and an increase in MIs (18 vs 11 for rates of 0.65 vs 0.42 for etoricoxib and diclofenac respectively, a 50% increase of events in etoricxoib over diclofenac). On the other hand, although the total number of CNS events are the same the number of ischemic cerebrovascular strokes in higher in the diclofenac group vs etoricoxib (6 vs 3). There are also 3 PEs in diclofenac vs 1 in etoricoxib. These numbers are small and firm conclusions are difficult.

Never the less, if we compare cardiac event rates in the EDGE study and those in the NDA database, a number of conclusions can be reached. For example, cardiac event rates in the NDA database show etoricoxib 11 events in 1522 patient-years (rate 0.72) vs 2 events in 501 patient years (rate 0.40; this is combined diclofenac and ibuprofen; for diclofenac alone there are 447 patient-years of exposure for a rate of 0.45). In either analysis there is an excess of cardiac events in the etoricoxib group.

Figure:

Kaplan-Meier Estimates of Cumulative Incidence for
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
Events Within 14 Days After Study Therapy Discontinuation



# Patients at Risk							
Etoricoxib 90 mg	3593	3155	2866	2617	2463	2347	1118
Diclofenac Sodium 150 mg	3518	3037	2719	2424	2255	2123	990

Note: 1 event in etoricoxib 90 mg occurred after the last shown time point. All events are included in the analysis.

Data Source: [4.35]

Reviewers comments: note that the etoricoxib and diclofenac plots do not actually overlap until month 12 and that through out the study period (until month 12) there are more events in the etoricoxib group than in the diclofenac group.

Table :

Summary Statistics for New Ischemic Heart Disease events in the EDGE Study

Treatment	Number of Patients with an Event	Total Number Of Patients	Patient-Years at Risk	Rate per 100 Patient-Years	
				%	95% CI
Etoricoxib 90 mg	25	3319	2564	0.98	(0.59, 1.36)
Diclofenac 150 mg	19	3253	2384	0.80	(0.44, 1.15)

Includes events up to and including 14 days post therapy.
CI = Confidence Interval

Reviewers comments: As in the analysis of the NDA, there is an increase in the rate of new ischemic events in the EDGE study.

The next table shows data in regards to any ASA use and CV risk factors.

Table :

Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
Events Within 14 Days after Study Therapy Discontinuation
Subgroup Analysis by Risk Factor
Etoricoxib Versus Diclofenac

Subgroup	Treatment	n/N (%)	Rate*	Relative Risk (95%)
≥2 Cardiovascular Risk Factor‡				
High Risk	Etoricoxib	18/1188 (1.52)	1.95	0.85 (0.45, 1.61)
	Diclofenac	20/1191 (1.68)	2.27	
Not High Risk	Etoricoxib	16/2405 (0.67)	0.86	1.45 (0.66, 3.19)
	Diclofenac	10/2327 (0.43)	0.58	
Aspirin User§				
Aspirin User	Etoricoxib	17/1039 (1.64)	2.07	1.10 (0.53, 2.27)
	Diclofenac	13/970 (1.34)	1.88	
Not Aspirin User	Etoricoxib	17/2554 (0.67)	0.86	0.98 (0.50, 1.91)
	Diclofenac	17/2548 (0.68)	0.89	

n/N=the number of patients with events/total number of patients; CI=Confidence Interval.

* Number of events per 100 patient-years.

‡ Cardiovascular risk factors include history of diabetes, hypercholesterolemia, hypertension, family history of cardiovascular disease, and tobacco use.

§ Aspirin user was defined as patient who took any dose of aspirin, clopidogrel, clopidogrel bisulfate, ticlopidine, and ticlopidine hydrochloride for at least 50% of the time while on study therapy, and did not start any of these medications after a confirmed thrombotic CV event.

Data Source: [4.35]

Reviewers comments: there is little difference when overall CV SAEs are evaluated.

However, the next table analyzes CV events in more detail including by specific event, with and without ASA use, in populations at different risk for CV events.

Table :

Subgroup Summary of Confirmed Thrombotic Cardiovascular Serious Adverse Events by Class of Terms (Events within 14 Days after Study Therapy Discontinuation)

ASA Users[‡]	Etoricoxib 90 mg			Diclofenac Sodium 150 mg		
Subgroup/ Confirmed Adjudicated Event	n(%)[‡]	Rate[¶]	95% CI	n(%)[‡]	Rate[¶]	95% CI
≥ 2 cardiovascular risk factors[‖]	N=493 390 Patient-Years			N=471 352 Patient-Years		
Total number of patients with Endpoint	10 (2.03)	2.56	(1.23 , 4.71)	12 (2.55)	3.41	(1.76 , 5.95)
Cardiac Events	7 (1.42)	1.79	(0.72 , 3.70)	8 (1.70)	2.27	(0.98 , 4.48)
Acute myocardial infarction	4 (0.81)	1.02	(0.28 , 2.62)	5 (1.06)	1.42	(0.46 , 3.31)
Unstable angina pectoris	3 (0.61)	0.77	(0.16 , 2.25)	3 (0.64)	0.85	(0.18 , 2.49)
Cerebrovascular Events	3 (0.61)	0.77	(0.16 , 2.25)	3 (0.64)	0.85	(0.18 , 2.49)
Fatal ischemic cerebrovascular stroke	1 (0.20)	0.26	(0.01 , 1.43)	0 (0.00)	0.00	---
Ischemic cerebrovascular stroke	1 (0.20)	0.26	(0.01 , 1.43)	2 (0.42)	0.57	(0.07 , 2.05)
Transient ischemic attack	1 (0.20)	0.26	(0.01 , 1.43)	2 (0.42)	0.57	(0.07 , 2.05)
Peripheral Vascular Events	0 (0.00)	0.00	---	1 (0.21)	0.28	(0.01 , 1.58)
Peripheral arterial thrombosis	0 (0.00)	0.00	---	1 (0.21)	0.28	(0.01 , 1.58)
< 2 cardiovascular risk factors[‖]	N=546 429 Patient-Years			N=499 341 Patient-Years		
Total number of patients with Endpoint	7 (1.28)	1.63	(0.66 , 3.36)	1 (0.20)	0.29	(0.01 , 1.63)
Cardiac Events	5 (0.92)	1.16	(0.38 , 2.72)	1 (0.20)	0.29	(0.01 , 1.63)
Acute myocardial infarction	3 (0.55)	0.70	(0.14 , 2.04)	0 (0.00)	0.00	---
Sudden cardiac death	1 (0.18)	0.23	(0.01 , 1.30)	0 (0.00)	0.00	---
Unstable angina pectoris	1 (0.18)	0.23	(0.01 , 1.30)	1 (0.20)	0.29	(0.01 , 1.63)
Cerebrovascular Events	1 (0.18)	0.23	(0.01 , 1.30)	0 (0.00)	0.00	---
Ischemic cerebrovascular stroke	1 (0.18)	0.23	(0.01 , 1.30)	0 (0.00)	0.00	---
Peripheral Vascular Events	1 (0.18)	0.23	(0.01 , 1.30)	0 (0.00)	0.00	---
Peripheral venous thrombosis	1 (0.18)	0.23	(0.01 , 1.30)	0 (0.00)	0.00	---

Table :

Subgroup Summary of Confirmed Thrombotic Cardiovascular Serious Adverse Events by Class of Terms (Events within 14 Days after Study Therapy Discontinuation)

ASA Non Users[1]	Etoricoxib 90 mg			Diclofenac Sodium 150 mg		
Subgroup[2] Confirmed Adjudicated Event	n(%)[3]	Rate[4]	95% CI	n(%)[3]	Rate[4]	95% CI
≥ 2 cardiovascular risk factors[‖]	N=695 531 Patient-Years			N=720 528 Patient-Years		
Total number of patients with Endpoint	8 (1.15)	1.51	(0.65 , 2.97)	8 (1.11)	1.52	(0.65 , 2.99)
Cardiac Events	8 (1.15)	1.51	(0.65 , 2.97)	6 (0.83)	1.14	(0.42 , 2.48)
Acute myocardial infarction	6 (0.86)	1.13	(0.41 , 2.46)	2 (0.28)	0.38	(0.05 , 1.37)
Sudden cardiac death	1 (0.14)	0.19	(0.00 , 1.05)	1 (0.14)	0.19	(0.00 , 1.06)
Unstable angina pectoris	1 (0.14)	0.19	(0.00 , 1.05)	3 (0.42)	0.57	(0.12 , 1.66)
Cerebrovascular Events	0 (0.00)	0.00	---	2 (0.28)	0.38	(0.05 , 1.37)
Ischemic cerebrovascular stroke	0 (0.00)	0.00	---	2 (0.28)	0.38	(0.05 , 1.37)
Peripheral Vascular Events	1 (0.14)	0.19	(0.00 , 1.05)	0 (0.00)	0.00	---
Peripheral venous thrombosis	1 (0.14)	0.19	(0.00 , 1.05)	0 (0.00)	0.00	---
< 2 cardiovascular risk factors[‖]	N=1859 1439 Patient-Years			N=1828 1386 Patient-Years		
Total number of patients with Endpoint	9 (0.48)	0.63	(0.29 , 1.19)	9 (0.49)	0.65	(0.30 , 1.23)
Cardiac Events	6 (0.32)	0.42	(0.15 , 0.91)	4 (0.22)	0.29	(0.08 , 0.74)
Acute myocardial infarction	5 (0.27)	0.35	(0.11 , 0.81)	4 (0.22)	0.29	(0.08 , 0.74)
Unstable angina pectoris	1 (0.05)	0.07	(0.00 , 0.39)	0 (0.00)	0.00	---
Cerebrovascular Events	3 (0.16)	0.21	(0.04 , 0.61)	2 (0.11)	0.14	(0.02 , 0.52)
Ischemic cerebrovascular stroke	1 (0.05)	0.07	(0.00 , 0.39)	2 (0.11)	0.14	(0.02 , 0.52)
Transient ischemic attack	2 (0.11)	0.14	(0.02 , 0.50)	0 (0.00)	0.00	---
Peripheral Vascular Events	1 (0.05)	0.07	(0.00 , 0.39)	3 (0.16)	0.22	(0.04 , 0.63)
Pulmonary embolism	1 (0.05)	0.07	(0.00 , 0.39)	3 (0.16)	0.22	(0.04 , 0.63)

Note: patients with multiple events may be counted more than once in different terms, but only once in each term.

[1]An ASA user were defined as patients using 'aspirin', 'clopidogrel', 'clopidogrel bisulfate' 'ticlopidine' and 'ticlopidine hydrochloride' for ≥ 50% of the time when they were on study medication. There were no restrictions placed on dose of these medications. Patients who started use of aforementioned meds after a confirmed CV event were not considered aspirin users.

[3]: Crude Incidence (n/N*100) ; [4]: Events per 100 Patient-Years

[‖]Cardiovascular risk factors include history of diabetes, history of hypercholesterolemia, history of hypertension, family history of cardiovascular disease, and tobacco use.

Reviewers comments: The table presents an important subset analysis. The results of this analysis of CV events in ASA users is somewhat inconsistent. If ASA use protects users of etoricoxib against CV events then the data for the ASA users and >2 CV risk factor group makes sense, in that there appears to be equal numbers of cardiac events in both the etoricoxib and diclofenac users. However, there appears to be more CV events in ASA users with <2 CV risk factors who also received etoricoxib. The possibility that with multiple analyses this is just a chance occurrence, cannot be ruled out.

On the other hand, the data in the non-ASA users appears to be internally consistent, in that in the group of non-ASA users with >2 CV risk factors there appears to be an excess of CV events in the etoricoxib users (especially MIs), while in the non-ASA users with <2 CV risk factors (which would be a low risk group) there is no excess of CV events. Adding up all the cardiac events, there are 14 in the etoricoxib group vs 10 in diclofenac; looking just at MIs, there are 11 in the etoricoxib group vs 6 in the diclofenac group. Both of these analyses demonstrate an increase of 40% to 80% of events in the etoricoxib vs diclofenac groups. The apparent increase in CNS and peripheral events in the diclofenac group is not consistent with data from the NDA and the number of events in small.

Other CV events (CHF, pulmonary edema)

Table : CHF adverse experiences, 6-12 week placebo controlled population

Treatment group	Placebo	Etoricoxib 60 mg	90 mg	120 mg	Naproxen 1000 mg	Ibuprofen 2400 mg
Frequency of patient with AEs	0/1767 (0)	3/896 (0.3)	5/1238 (0.4)	2/664 (0.3)	1/1133 (0.1)	0/226 (0)

Reviewers comments: Results of the analysis of adverse experiences of CHF, pulmonary edema, and left cardiac failure in the one year population showed 0 (0.0%), 2 (0.4%), 3 (0.4%), 2 (0.9%), and 2 (0.2%) patients with these adverse experiences in the etoricoxib 30-, 60-, 90-, and 120-mg and naproxen groups, respectively.

In addition to the above, the sponsor provided a table of numbers of unique discontinuations due to "CHF" across the entire NDA. There were a total of 5 cases of "CHF" in the etoricoxib 90 mg group (patient-years of exposure were 1720) and 1 in the 120 mg group (pt-years 907) vs 0 for diclofenac and ibuprofen and 1 for naproxen (patient-years of exposure 1660). Combining the 90 and 120 mg group gives the following: etoricoxib 6 cases (2627 patient years) vs 1 naproxen case (1660 patient-years). There appears to be an excess of discontinuations in relation to "CHF".

Furthermore, the sponsor provided a table of numbers of unique SAEs due to "CHF" across the entire NDA. There were a total of 7 cases of "CHF" in the etoricoxib 90 mg group (patient-years of exposure were 1720) and 1 in the 120 mg group (pt-years 907) vs 1 for diclofenac and 0 ibuprofen and 4 for naproxen (patient-years of exposure

1660). Combining the 90 and 120 mg group gives the following: 8 etoricoxib cases (2627 patient years) vs 4 naproxen cases (1660 patient-years). There appears to be a slight excess of SAEs in relation to "CHF" in the etoricoxib treatment group.

EDGE study

Number of patients with CHF, pulmonary edema, or cardiac failure adverse experiences

Adverse experience	Etoricoxib 90 mg (N=3593)	Diclofenac 150 mg (N=3518)
	N (%)	N (%)
Incidence of CHF, pulmonary edema, or cardiac failure	**14 (0.4)**	**6 (0.2)**
Cardiac failure	**1**	**0**
Cardiac congestive failure	**12**	**6**
PND	**1**	**0**

Reveiwers comments: the EDGE study confirms the results from the NDA.

Summary of CV safety:

This section summarizes the issue of CV safety with use of etoricoxib. In each instance, results will be reviewed based on comparisons between etoricoxib and placebo, naproxen, and non-naproxen NSAIDS for each endpoint (deaths, SAEs, etc). The results appear to demonstrate that etoricoxib is worse than each comparator. For example, comparisons to naproxen demonstrate an increase in events related to etoricoxib; for comparisons to placebo, there is again an increase in events related to etoricoxib, although the conclusions are limited by the relatively small number of events and the relatively short duration of exposure. However, the consistency of the data in all analyses should also be considered.

For CV related deaths there appears to be an excess of cases due to etoricoxib compared to placebo although the exposure to placebo is limited. However, the data related to naproxen clearly shows an excess of CV mortality related to etoricoxib (and this is consistent with comparisons of naproxen to rofecoxib in other studies). The explanation for these results is not clear and may or may not be related to a protective effect of naproxen (not demonstrated).

Comparisons to non-naproxen NSAIDs are important. Superficially the rates of CV related deaths for the non-naproxen NSAIDs and etoricoxib are similar, and this is certainly the case for data from the EDGE trial. However, in the NDA the 2 deaths in the non-nparoxen NSAID group occurred at greater than 3 years while the deaths in the etoricoxib group occurred at earlier time points. Comparability of events in the EDGE study (and differences from data in the NDA database) may be a reflection of differences in the study design and conduct, which have been discussed earlier. Two main concerns are that the EDGE study allowed subjects who were previously on Cox-2 inhibitors and the high % of those on ASA (which may be protective of CV events even in the context of a Cox-2 inhibitor). For CV related SAEs there is again an increase in events related to etoricoxib compared to placebo and naproxen. This is also true for comparisons to diclofenac (see part II up to week 52).

If we now turn to an analysis of adjudicated events, it appears that overall there is little if any difference in pooled CV/TE events (MI, CVA, TIA etc). However, when one examines specifically cardiac events there remains an increase in events associated with the use of etoricoxib whether one compares to placebo or naproxen. This excess remains when comparing etoricoxib to diclofenac especially given the fact that diclofenac events occurred mostly after 3 years (see KM curves for CV events). Lastly, an analysis of "New ischemic heart disease" reveals and increase in events related to etoricoxib when compared to placbo, naproxen or non-naproxen NSAIDs.

The EDGE study compared etoricoxib to diclofenac. The overall results for mortality and CV/TE events are similar for both drugs. Closer inspection of cardiac events, however, again reveals that there are more events in etoricoxib than diclofenac, and this is especially true for MIs. However, there are more ischemic strokes in the diclofenac group although the number of events is small, which makes interpretation difficult.

Analyses in the NDA with or without ASA suggest that use of ASA may be protective of CV events (see table of analysis by ASA use, etoricoxib vs naproxen), although this may not be supported by data in the EDGE study. However the comparators are different.

Finally, an analysis of events occurring during the placebo period suggests that therisk of CV events in the 60 mg dose group is similar to placebo, while the increased rate of CV events is due almost entirely to the 90 mg dose.

V. GI events analysis

The sponsor has divided the GI section into several areas. These include: 1) an analysis of clinically important outcomes including perforations, symptomatic ulcers, and bleeds (PUBs; the use of the term POBs replaces symptomatic ulcers with perforations and is considered a clinically complicated PUB, see next Table below); 2) endoscopy studies to evaluate for ulcer formation; 3) GI tolerability manifest for example as new use of gastroprotective agents etc (for further discussion of these endpoint, see below); 4) and fecal blood loss. Only clinically important GI events, so called PUBs, will be presented here. The comparisons are between etoricoxib and NSAIDS combined or placebo. Additional subset analyses examine individual NSAIDs (naproxen and diclofenac).

i. PUBs

Table: comparison between etoricoxib and non-selective NSAID analysis of PUB events which occurred within one year of treatment (sponsor table E-165)

Treatment	n/N (%)	Person-Years	Rate[1]	95% CI for Rate	Relative Risk[2] (RR)	95% CI for RR
Confirmed PUBs (Primary Endpoint)						
Etoricoxib[3]	28/3226 (0.87)	2264.42	1.24	(0.82, 1.79)	0.47	(0.29, 0.77)
Nonselective NSAIDs Combined	39/2215 (1.76)	1328.40	2.94	(2.09, 4.01)		
Confirmed Plus Unconfirmed PUBs (Secondary Endpoint)						
Etoricoxib[3]	35/3226 (1.08)	2264.13	1.55	(1.08, 2.15)	0.50	(0.32, 0.79)
Nonselective NSAIDs Combined	46/2215 (2.08)	1327.55	3.47	(2.54, 4.62)		
Confirmed Clinically Complicated PUBs (Exploratory Endpoint)						
Etoricoxib[3]	12/3226 (0.37)	2265.94	0.53	(0.27, 0.93)	0.69	(0.31, 1.53)
Nonselective NSAIDs Combined	13/2215 (0.59)	1330.64	0.98	(0.52, 1.67)		
Confirmed Plus Unconfirmed Clinically Complicated PUBs						
Etoricoxib[3]	15/3226 (0.46)	2265.84	0.66	(0.37, 1.09)	0.73	(0.35, 1.52)
Nonselective NSAIDs Combined	15/2215 (0.68)	1330.58	1.13	(0.63, 1.86)		

[1] Number of events per 100 person-years.
[2] 60 mg etoricoxib.
[3] Relative risk to Nonselective NSAIDs Combined by Cox Model.

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Reviewers comments: the overall event rates demonstrate that the relative risk of a PUB for etoricoxib is about one half that of nonselective NSAIDs combined However, additional subsets including individual NSAIDs, are examined below.

Table : Analysis of confirmed PUBs which occurred during the first year of treatment (analysis by drug, dose,

indication)

Treatment	n/N (%)	Mean Duration (Day)	Person-Year	Rate[‡]
OA Studies (Protocols 007+018+019+805)				
Etoricoxib 60 mg	5/950 (0.5)	233.6	607.62	0.8
Etoricoxib 60 mg/90 mg/60 mg[†]	0/50 (0.0)	282.5	38.67	0.0
Etoricoxib 90 mg/90 mg/60 mg[†]	1/112 (0.9)	253.0	77.59	1.3
Combined Etoricoxib Group	6/1112 (0.5)	237.8	723.88	0.8
Diclofenac 150 mg	1/362 (0.3)	109.9	108.97	0.9
Naproxen 1000 mg	18/476 (3.8)	277.3	361.33	5.0
RA Studies (Protocols 010+024+025)				
Etoricoxib 60 mg/90 mg[§]	2/170 (1.2)	320.9	149.35	1.3
Etoricoxib 90 mg	7/756 (0.9)	318.0	658.23	1.1
Etoricoxib 90 mg/120 mg[§]	4/343 (1.2)	314.3	295.20	1.4
Etoricoxib 120 mg	3/120 (2.5)	323.1	106.15	2.8
Combined Etoricoxib Group	16/1389 (1.2)	317.9	1208.93	1.3
Diclofenac 150 mg	1/130 (0.8)	328.1	116.77	0.9
Naproxen 1000 mg	15/650 (2.3)	296.7	527.94	2.8
RA/OA Endoscopy Study (Protocol 026)				
Etoricoxib 120 mg	3/251 (1.2)	88.8	61.04	4.9
Naproxen 1000 mg	2/244 (0.8)	83.7	55.92	3.6
OA Endoscopy Study (Protocol 029)				
Etoricoxib 120 mg	1/221 (0.5)	90.5	54.79	1.8
Ibuprofen 2400 mg	1/226 (0.4)	87.3	53.99	1.9
AS Study (Protocol 032)				
Etoricoxib 90 mg	0/129 (0.0)	317.0	111.97	0.0
Etoricoxib 120 mg	2/124 (1.6)	305.8	103.81	1.9
Combined Etoricoxib Group	2/253 (0.8)	311.5	215.78	0.9
Naproxen 1000 mg	1/127 (0.8)	297.6	103.49	1.0

[‡] Events per 100 person-years.
[†] Part I/Part II/Part III treatments.
[§] Part I/Part II treatments.

Reviewers comments: This table is very enlightening. The results of previous analyses are clearly driven almost entirely by comparisons of etoricoxib to naproxen. Furthermore there is little difference between diclofenac and etoricoxib or between ibuprofen and etoricoxib. In addition, etoricoxib 120 mg (the highest recommended dose for actue pain) is comparable to naproxen 1000 mg in most studies with the exception of the OA studies combined where the rate of PUBs for naproxen appears unusually high (5.0 vs 1-3.6 in other indications). Results for confirmed and unconfirmed PUBS are similar and are not shown. In addition, the overall analysis (shown previously) also includes the 60 mg dose of etoricoxib which is the lowest dose proposed at this time and which contributes to the apparent improved safety profile.

Another useful comparison is between ASA and non-ASA users since etoricoxib (and other Cox-2 inhibitors) do not have any effect on platelets.

Table : ASA users vs non-users active comparator controlled data set, PUBs during the first year of treatment

Subgroup	Treatment	n/N (%)	Exposure Time (Year)	Rate[†] (95%CI)	Relative Risk to NSAID[‡] (95%CI)
Endpoint: Confirmed PUB (p[§] = NA)					
Non-ASA User	Etoricoxib Combined	23/3103 (0.7)	2189.52	1.05 (0.67, 1.58)	0.38 (0.23, 0.65)
	NSAIDs Combined	39/2115 (1.8)	1282.08	3.04 (2.16, 4.16)	
ASA User	Etoricoxib Combined	5/123 (4.1)	74.89	6.68 (2.17, 15.58)	NA
	NSAIDs Combined	0/100 (0.0)	46.32	0.00 (0.00, 7.96)	

[†] Events per 100 person-year.
[‡] By proportional hazards model.
[§] For testing of treatment by subgroup interaction. It was NA due to no events in one of the treatment by subgroup cells.

Reviewers comments: any differences in PUBs comparing etoricoxib with other NSAIDs is due entirely to the non-ASA user group, although the exposure time for ASA plus NSAIDs combined is low and there were no events seen. These results are consistent with the results for the ASA analysis in the EDGE study (see below).

EDGE study/ GI analysis

a. PUBs

Summary of Upper GI Events
(Modified Intention-to-Treat)

	Etoricoxib 90 mg (N=3593)			Diclofenac 150 mg (N=3518)		
	n (%)[1]	Rate[2]	95% CI	n (%)[1]	Rate[2]	95% CI
Confirmed Upper GI Events						
Number of patients with at least one Upper GI event	31 (0.86)	1.11	(0.72, 1.50)	29 (0.81)	1.11	(0.71, 1.51)
Perforation	0 (0.00)	--	--	0 (0.00)	-	
Gastric ulcer	21 (0.58)	0.75	(0.43, 1.07)	17 (0.47)	0.65	
Duodenal ulcer	10 (0.28)	0.36	(0.14, 0.58)	13 (0.36)	0.50	
Obstruction	0 (0.00)	--	--	0 (0.00)	-	
Upper GI bleed	17 (0.47)	0.61	(0.32, 0.90)	13 (0.36)	0.50	
Confirmed and Unconfirmed Upper GI Events						
Number of patients with at least one Upper GI event	39 (1.09)	1.40	(0.96, 1.83)	35 (0.97)	1.34	(0.90, 1.78)
Perforation	0 (0.00)	--	--	0 (0.00)	-	
Gastric ulcer	23 (0.64)	0.82	(0.49, 1.16)	18 (0.50)	0.69	
Duodenal ulcer	10 (0.28)	0.36	(0.14, 0.58)	13 (0.36)	0.50	
Obstruction	1 (0.03)	0.04	(0.00, 0.11)	0 (0.00)	-	
Upper GI bleed	27 (0.75)	0.97	(0.60, 1.33)	23 (0.64)	0.88	

Includes events up to and including the 14-day poststudy period.
Note: Patients with multiple events may be counted more than once in different terms, but only once in each term.
PYR = Patient-years at risk; CI=Confidence Interval.
[1] Crude incidence rate (%) = (n/N)x 100.
[2] Rate = Events per 100 patient-years = (n/PYR)x 100.

Data Source: [4.1; 4.2]

Reviewers comments: there is essentially no difference between etoricoxib and diclofenac for PUBs.

The next table shows an analysis of GI events in ASA and non-ASA users.

Table :

Subgroup of Aspirin Analysis of Confirmed Upper GI Events
Number of Patients With at Least One Upper GI Event
(Modified Intention-to-Treat)

Treatment	n/N (%)[†]	Rate[‡]	95% CI
Actual Concomitant Aspirin Use			
Yes			
Etoricoxib 90 mg	19/1062 (1.79)	2.27	(1.26, 3.28)
Diclofenac 150 mg	14/ 979 (1.32)	2.00	(0.96, 3.03)
No			
Etoricoxib 90 mg	12/2531 (0.47)	0.61	(0.27, 0.96)
Diclofenac 150 mg	15/2539 (0.59)	0.79	(0.39, 1.18)

Includes events up to and including a 14 day post study period.
PYR = Patient-years at risk; CI= Confidence Interval.
[†] Crude incidence rate (%) = (n/N) x 100.
[‡] Rate = Events per 100 patient-years = (n/PYR)x 100.

Data Source: [4.1; 4.2]

Reviewers comments: rates for ASA users is higher than non-users as might be expected. Any small benefit of etoricoxib over diclofenac in terms of PUBs, for non-ASA users, is lost in ASA users.

Table :

Cumulative Incidence of New Use of GPA Medications
(Modified Intention-to-Treat)

Treatment	n/N (%)	Patient-Years at Risk	Rate[‡]	95% CI for Rate
Etoricoxib 90 mg	348/3417 (10.2)	2331	14.9	(13.48, 16.38)
Diclofenac 150 mg	331/3348 (9.9)	2175	15.2	(13.71, 16.72)

Overall Summary Statistics for Between-Treatment Comparison

Treatment	Relative Risk[§]	95% CI for Relative Risk[§]	p-Values	
			Cox PH[§]	Log Rank
Etoricoxib vs. Diclofenac	1.01	(0.86, 1.17)	0.944	0.944

n/N=the number of patients with events/total number of patients; CI = Confidence Interval.
[‡] Number of events per 100 patient-years.
[§] Relative risk from the Cox proportional hazards (PH) model with treatment in the model.

Data Source: [4.1]

Reviewers comments: there was no difference in the new use of GPA medications.

GI summary and conclusions:

One of the main reasons for developing the Cox-2 inhibitors was the hypothesis that they would show an improved safety profile compared to traditional NSAIDs in regards to GI safety. What is clearly evident from the data presented here is that any comparisons of GI safety cannot be extrapolated to all NSAIDs. While the data comparing etoricoxib to naproxen support the improved GI safety profile, data comparing etoricoxib to other NSAIDs such as diclofenac or ibuprofen, however, do not. Data for diclofenac use in regards to PUBs, are consistent between the NDA data set and the EDGE study. Furthermore, the use of ASA for CV prophylaxis appears to negate any beneficial effect of etoricoxib on GI safety, and this is supported by data from both the NDA and the EDGE study.

Having said that, it is also important to point out that not all comparisons of etoricoxib to naproxen were favorable to etoricoxib, in terms of GI safety. For example, the greatest benefit seen with etoricoxib was in the OA studies for PUBs, and not in RA studies. Furthermore, the favorable comparisons depend on the dose of etoricoxib chosen for comparison. For example, the 120 mg dose of etoricoxib and the 1000 mg dose of naproxen are similar in terms of GI events. With "dose creep" it is possible that patients who need additional pain relief will use the higher dose approved in the label (even though this dose is for acute analgesia) which is the 120 mg dose.
It should also be pointed out that endoscopy data and fecal blood loss data support the improved GI safety profile of etoricoxib, although the clinical significance of these comparisons is not clear. The sponsor places much of this data in the label. However, if this data is ultimately included in the label, it should be tempered with the results of the clinically important outcomes including the PUB results. Improved GI tolerability depends on GI symptoms and may be useful for physicians and patients to know, but does not appear to predict clinically important GI outcomes and again, depends on the comparator, the dose of etoricoxib chosen for comparison, and use of ASA.

In conclusion, the GI advantage of etoricoxib is limited to comparisons to naproxen, and at that, depends on several factors including the doses chosen for comparison. Any suggestion of improved GI safety in the label should be tempered with data for other comparators and ASA use.

VI. Hypertension

i. Data from the NDA

Table :

Summary of Hypertension-Related Adverse Experiences: Absolute Incidences
12-Week Placebo-Controlled Population

	Placebo (N=1011)		Etoricoxib 60 mg (N=658)		Etoricoxib 90 mg (N=889)		Naproxen 1000 mg (N=790)	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients with one or more hypertension-related adverse experiences	**21**	**(2.1)**	**31**	**(4.7)**	**41**	**(4.6) ****	**30**	**(3.8)**
Blood Pressure Increased	3	(0.3)	3	(0.5)	9	(1.0)	4	(0.5)
Diastolic Hypertension	0	(0.0)	1	(0.2)	1	(0.1)	0	(0.0)
Hypertension	16	(1.6)	26	(4.0)	30	(3.4)	23	(2.9)
Hypertensive Crisis	1	(0.1)	1	(0.2)	0	(0.0)	2	(0.3)
Systolic Hypertension	1	(0.1)	1	(0.2)	1	(0.1)	0	(0.0)
Uncontrolled Hypertension	0	(0.0)	0	(0.0)	1	(0.1)	1	(0.1)
Patients discontinued due to a hypertension-related adverse experience	**0**	**(0.0)**	**2**	**(0.3)**	**3**	**(0.3)**	**3**	**(0.4)**

Reviewers comments: There is a slight increase in hypertension related AEs in the etoricoxib group over placebo and naproxen treated subjects.

EDGE study

Table :

Number (%) of Patients With Specific Clinical Adverse Experiences: Hypertension-Related Adverse Experiences

	Etoricoxib 90 mg (N=3593)		Diclofenac 150 mg (N=3518)	
	n	(%)	n	(%)
Hypertension				
Number (%) of patients:				
With a hypertension-related adverse experience	422	(11.7)	209	(5.9)
With a drug-related[†] hypertension-related adverse experience	296	(8.2)	135	(3.8)
With a serious hypertension-related adverse experience	5	(0.1)	2	(0.1)
With a history of hypertension who also had a hypertension-related adverse experience	238	(6.6)	129	(3.7)
With an hypertension-related adverse experience associated with a systolic ≥180 mm Hg or a diastolic ≥110 mm Hg	69	(1.9)	30	(0.9)

Includes adverse experiences up to and including a 14 day poststudy period. [†] Assessed by the investigator to be possibly, probably, or definitely drug-related.

Data Source: [3.13; 4.1; 4.2]

Reviewers comments: The results of the EDGE study more clearly demonstrate an effect of etoricoxib on hypertension related AEs as compared to diclofenac.

Table :

Number (%) of Patients Who Discontinued Due to Hypertension-Related Clinical Adverse Experiences

Adverse Experience	Etoricoxib 90 mg (N=3593) n (%)	Diclofenac 150 mg (N=3518) n (%)	Difference in Proportions Estimate	95% CI
Discontinuations due to any hypertension-related adverse experiences	81 (2.3)	23 (0.7)	1.60	(1.06, 2.18)
Blood pressure increased	28 (0.8)	5 (0.1)		
Hypertension	53 (1.5)	17 (0.5)		
Systolic hypertension	0 (0.0)	1 (0.0)		

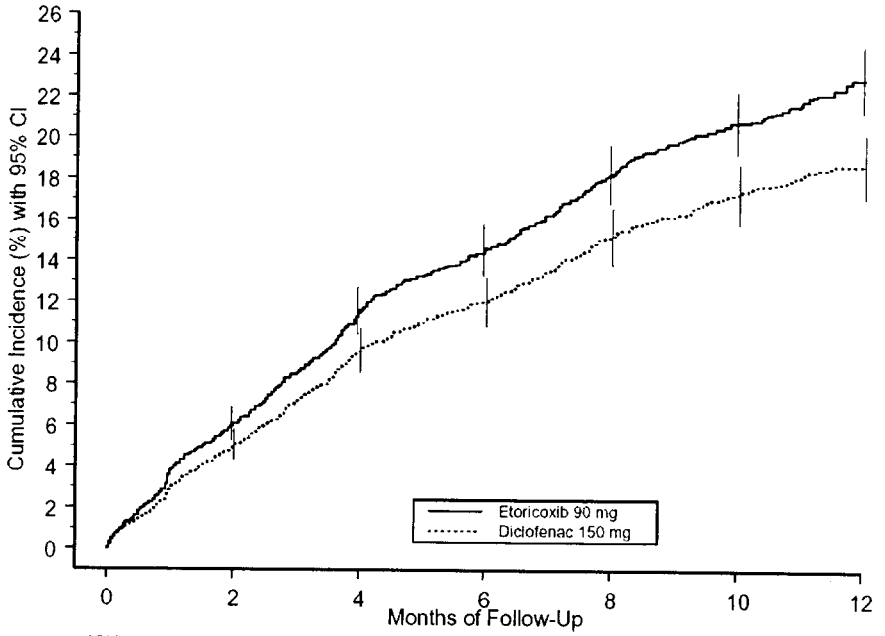
Although a patient may have had 2 or more adverse experiences, the patient is counted only once in the overall category. The same patient may appear in different categories.
Includes adverse experiences up to and including the End-of-Study Visit.
95% confidence interval (CI) is calculated by Wilson's Score Method.

Data Source: [3.13; 4.2]

Reviewers comments: Discontinuations related to hypertension due to etoricoxib are consistent with the previous data for AEs.

Figure:

Cumulative Incidence of New Use of Hypertension Medications



Patients at Risk							
Etoricoxib 90 mg	3593	2901	2479	2246	2024	1884	602
Diclofenac 150 mg	3518	2799	2359	2113	1894	1761	564

The rate (number of events per 100 patient years) of new hypertension medication use is 27.4 for etoricoxib and 22.3 for diclofenac (relative risk 1.24; $p<0.001$).

Summary of hypertension data:

There appears to be an increase in the incidence of hypertension in the etoricoxib group. However this depends in part, on the comparator chosen for analysis. For example, it is clear that compared to diclofenac there is a greater incidence of hypertension related AEs with etoricoxib. This is less so when etoricoxib is compared to naproxen. However, overall there appears to be an increase in hypertension related AEs in etoricoxib treated subjects.

VII. Summary:

The following conclusions can be reached:

1. Overall mortality is highest in the etoricoxib group in the NDA. Overall mortality in the EDGE study is comparable between etoricoxib and diclofenac.

2. Data from the NDA suggests a CV safety signal. This is present whether etoricoxib is compared to naproxen or non-naproxen NSAIDs. Given the limitations of the placebo comparisons, a number of analyses of the NDA data support the conclusion that there is an increase in CV events in the etoricoxib treated subjects compared to placebo. Data comparing OA and RA subjects is limited.

3. Data from the EDGE study, which involved only OA subjects, suggest that there is a signal for cardiac specific events when etoricoxib is compared to diclofenac, although an analysis of overall CV thromboembolic events is similar between the 2 drugs. There are limitations to the interpretation of the study due to issues related to design and conduct of the study which includes the extensive use of low dose ASA, and the allowance of previous Cox-2 use.

4. There is an increase in CHF related events in etoricoxib treated subjects in these studies.

5. There is a marginal GI advantage of etoricoxib which is mainly seen when etoricoxib is compared to naproxen in OA patients, and in general at the doses of 60 and 90 mg. This advantage is entirely lost in users of low dose ASA.

6. There is an increase in hypertension related AEs in etoricoxib treated subjects.

Choice of dose of etoricoxib and comparator appears to affect conclusions.

NDA 21-521/ IND 58,495
PREXIGE (COX189, lumiracoxib 100 mg tablets)

Regulatory History

Significant Date	Submission or meeting Type	Details
May 24, 1999	Pre-IND meeting	
August 12, 1999	IND filing date	400 mg and 200 mg tablets
February 23, 2000	GI safety meeting	
May 9, 2000	End of Phase 2 meeting	
December 7, 2001	Arthritis Advisory Committee	TARGET study design presented
December 13, 2001	Pre-NDA meeting	Novartis and FDA
April 30, 2002	Trade name consult Prexige	DMETS Recommended against Prexige
November 20, 2002	NDA filing date	Indication- symptomatic relief in the treatment osteoarthritis and rheumatoid arthritis; relief of acute pain; treatment of primary dysmenorrhea
September 2, 2003	DSMB interim analysis	Discussed hepatoxicity, GI, and cardiovascular adverse events
September 23, 2003	NDA Action date	Non approval for inadequate information, facilities, and extablished name not in compliance with USAN.
June 25, 2005	Special Protocol Assessment	SPA for 100 mg efficacy in hip and knee OA. Finally accepted December 2004.
July 1, 2004	TARGET study report submitted to IND	
October 31, 2004	Trade name consult Prexede	DMETS recommended against Prexede. DDAMC accepts Prexede.