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Glossary of Terms

Term	Definition
APPROVe	**A**denomatous **P**olyp **PR**evention **O**n **V**IOXX™ study. 3-year study in over 2500 patients with resected colon polyp.
APTC	**A**nti-**P**latelet **T**rialists' **C**ollaboration
APTC combined endpoint	myocardial infarction, stroke, or vascular death. Based on events confirmed by adjudication except for studies antedating the adjudication SOP
ASCVD	atherosclerotic cardiovascular disease
Clinical upper GI event	confirmed PUB
Complicated PUB	the subset of more severe PUBs: perforations, gastric outlet obstruction due to ulcer, and major upper GI bleeds
Complicated upper GI event	confirmed complicated PUB
Confirmed Thrombotic Cardiovascular serious adverse experience	a potential cardiac, cerebrovascular, or peripheral vascular arterial or venous thrombotic event that was confirmed by an external independent adjudication committee
Confirmed/unconfirmed complicated PUB	a complicated PUB confirmed (unconfirmed) by the external independent adjudication committee
Confirmed/unconfirmed PUB	a PUB confirmed (unconfirmed) by the external independent adjudication committee
EDGE study	**E**toricoxib vs. **D**iclofenac Sodium **G**astrointestinal Tolerability and **E**ffectiveness Trial (in Osteoarthritis patients)
EDGE II study	**E**toricoxib vs. **D**iclofenac Sodium **G**astrointestinal Tolerability and **E**ffectiveness Trial (in rheumatoid arthritis patients)
Investigator reported thrombotic cardiovascular serious adverse experience	an investigator report of a potential cardiac, cerebrovascular, or peripheral vascular arterial or venous thrombotic event
MEDAL Study	**M**ultinational **E**toricoxib and **D**iclofenac **A**rthritis **L**ong-term Study
PGI_2	Prostacyclin
PGI-M	prostacyclin metabolite: 2,3-dinor-6-keto-prostaglandin F1 alpha,
PUB	gastroduodenal **P**erforation, symptomatic gastroduodenal **U**lcer, or upper GI **B**leed
TXA_2	Thromboxane A_2
TXB_2	Thromboxane B_2

Executive Summary

Etoricoxib is a selective cyclooxygenase-2 (COX-2) inhibitor with efficacy in the treatment of a range of rheumatological and painful conditions. It is currently approved in 60 countries. In the United States, a New Drug Application (NDA) is under review by the Food and Drug Administration (FDA), with an approvable letter received in October 2004. The attached background document for the Coxib Advisory Committee Meeting provides an overview of the cardiovascular (CV) safety data on etoricoxib, as well as the available clinical information on efficacy, and gastrointestinal (GI) and renovascular safety. Studies currently ongoing to further assess CV safety are also discussed. The following provides a high-level summary of the information contained in the etoricoxib background document and, for ease of review, is cross-referenced to the appropriate section of the document.

SUMMARY

Clinical Pharmacology (Section 2)

Etoricoxib is rapidly and completely absorbed following oral administration with a time to peak plasma concentration (T_{max}) occurring at approximately 1 hour and an absolute bioavailability of approximately 100%. These properties likely contribute to etoricoxib's rapid onset of action. Its effective half-life of approximately 22 hours supports its recommended once daily dosing.

Efficacy (Section 3)

Etoricoxib has demonstrated efficacy in the treatment of patients with osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS), chronic low back pain (CLBP), acute gouty arthritis, and acute pain (postdental surgery pain, postorthopedic surgery pain and primary dysmenorrhea). In addition to providing pain relief in the acute and chronic setting (OA and CLBP), etoricoxib demonstrates anti-inflammatory properties that are comparable and in some cases, superior to nonselective NSAIDs (RA and AS). Etoricoxib extends the efficacy of selective COX-2 inhibitors to two new patient populations, namely patients with acute gouty arthritis and AS.

Gastrointestinal Safety and Tolerability (Section 4)

The etoricoxib gastrointestinal (GI) safety program was comprehensive and included studies of gastric mucosa prostaglandin synthesis, fecal blood loss, surveillance endoscopy and prespecified analyses of clinical upper GI events (gastroduodenal perforations, symptomatic gastroduodenal ulcers, and upper GI bleeds, [PUBs]) and GI tolerability. Overall, these findings supported the rationale for the development of etoricoxib as an alternative therapy with overall superior GI safety and tolerability compared to non-selective non-steroidal anti-inflammatory agents (NSAIDs).

Two endoscopy studies were carried out to assess cumulative rates by 12 weeks of endoscopic ulcers in patients taking etoricoxib 120 mg (1.3x the maximal recommended chronic dose), placebo or nonselective NSAIDS. One of these studies was conducted in

patients with OA, with ibuprofen 2400 mg daily as the active comparator, while the other study was conducted in patients with either OA or RA, with naproxen 1000 mg daily as the active comparator. In both studies, the rates of gastroduodenal ulcers (≥3 mm) by 12 weeks in the etoricoxib groups were significantly lower than the corresponding rates with treatment with the individual non-selective NSAIDs. In both studies, etoricoxib 120 mg showed higher rates of ulcers by 12 weeks than placebo.

Data regarding the incidence of PUBs are summarized from a pooled analysis of the active controlled portions of Phase IIb/III studies of at least 4 weeks in duration. These studies are referred to collectively as the chronic exposure studies, and also form the basis for the pooled analysis of CV events (Section 6) and the review of renovascular safety data (Section 5). PUBs were adjudicated by an external committee according to prespecified criteria for confirmation and classification, including identification of clinically complicated events. The adjudication process was identical to the procedures used for the rofecoxib development program. The analysis includes complete data from a total of 5441 patients. In this analysis, there was a statistically significant 52% reduction in the rate of confirmed PUBs with etoricoxib (all doses ≥60 mg combined) versus non-selective NSAIDs combined. The rate per 100 patient-years of confirmed PUBs was 1.00 for the etoricoxib group versus 2.47 for the combined NSAIDs group (relative risk of 0.48, with 95% confidence interval (CI) for the relative risk of 0.32, 0.73). The magnitude of the risk reduction for clinically complicated PUB events was consistent with these results. The results in the nonselective NSAID group were mostly driven by naproxen.

An additional study, the EDGE study (Etoricoxib vs. Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness Trial), was performed to assess the GI tolerability of etoricoxib 90 mg versus diclofenac in 7111 OA patients. The study demonstrated a statistically significant relative risk of 0.50 (95% CI for the relative risk of 0.43, 0.58) favoring etoricoxib for the primary study endpoint (rates of patient discontinuing for combined clinical and laboratory GI adverse experiences). A benefit was observed in each component of the primary study endpoint (clinical GI adverse experiences, laboratory GI adverse experiences) when evaluated separately. An exploratory analysis of PUBs from the EDGE study showed similar rates with etoricoxib versus diclofenac. These data are confounded by unrestricted aspirin and gastroprotective agent use. Rates of gastroduodenal ulcers were higher on etoricoxib and diclofenac used concomitantly with aspirin compared to the use of either therapy alone. In non-aspirin patients, there was a numerically lower rate on etoricoxib than diclofenac, but the difference was not statistically significant.

Renovascular Safety (Section 5)

Renovascular effects (edema, congestive heart failure [CHF], and hypertension) are known dose-related effects of COX inhibition and have been observed with all nonselective NSAIDs [1; 2] and selective COX-2 inhibitors [3; 4; 5], and are reflected in NSAID class labeling. To evaluate the clinical impact of potential

renovascular effects with etoricoxib, a composite of edema-related and hypertension-related adverse experiences was defined. The composite terms were prespecified to provide greater precision than the individual adverse experience terms when comparing treatment groups. In addition, CHF adverse experiences were evaluated in a prespecified manner.

Two populations were designed to evaluate the safety of etoricoxib compared with placebo and the longer-term safety of etoricoxib compared with approved and commonly used NSAID therapies: the Placebo-Controlled Population (comprised of data from the placebo-controlled periods of the chronic exposure studies) and the 1-Year Continuous Exposure, Active-Comparator-Controlled Population (comprised of data over a continuous, 52-week treatment period from the subset of chronic exposure studies which extended at least 1 year in duration). In addition, the renovascular safety profile of etoricoxib from the EDGE study is reviewed.

Overall, the data indicated that etoricoxib was associated with the development of edema-related and hypertension-related adverse experiences generally consistent with the effects of fluid retention observed for NSAIDs. Edema-related adverse experiences generally occurred early, and were mild, transient, and infrequently led to discontinuations. CHF adverse experiences were rare in all patient populations, including the elderly. A shallow dose response was observed in the incidence of hypertension-related adverse experiences on etoricoxib, with an overall incidence on etoricoxib that was generally similar to naproxen and slightly lower than ibuprofen. Most of the hypertension adverse experiences were mild to moderate in intensity and discontinuation due to hypertension adverse experiences was infrequent.

In the EDGE study, the GI tolerability of etoricoxib 90 mg in OA was compared with that of diclofenac 150 mg. This dose of etoricoxib is 50% greater than the highest recommended OA dose (60 mg). The incidence of edema-related adverse experiences and discontinuations resulting from edema-related adverse experiences were low and similar between etoricoxib and diclofenac. None of the adverse experiences were considered serious. CHF was low in both treatment groups. A significantly higher incidence of hypertension-related adverse experiences was observed for etoricoxib 90 mg than for diclofenac 150 mg. The percentage of patients discontinuing from the study due to hypertension-related adverse experiences on etoricoxib and diclofenac was low, but significantly different favoring diclofenac.

Cardiovascular Safety (Section 6)

A Cardiovascular Adjudication Standard Operating Procedure (CV Adjudication SOP) was initiated in the second half of 1998, and used throughout the entire etoricoxib clinical development program. This was the same SOP used in the rofecoxib development program. The analysis of CV outcomes in trials of etoricoxib as described in the SOP was designed to examine the combined incidence of CV events across a broad range of patients in all trials with chronic dosing (defined as duration of at least 4 weeks).

The primary endpoint used in the pooled analysis for etoricoxib was Confirmed Thrombotic Cardiovascular Serious Adverse Experiences. This endpoint represents the composite of all adverse experiences which were confirmed to be thrombotic based on the adjudication process and includes terms such as unstable angina, myocardial infarction, ischemic stroke, and transient ischemic attacks, but does not include fatal hemorrhagic deaths or hemorrhagic stroke. This endpoint was chosen as primary because it represents the largest amount of adjudicated data for etoricoxib, and thus allows for the most precise estimate. The Anti-Platelet Trialists' Combined (APTC) endpoint was also evaluated and provided consistent results. All deaths reported during etoricoxib clinical trials were also adjudicated.

An evaluation of thrombotic CV safety using the Confirmed Thrombotic CV serious adverse experience endpoint is presented based on data pooled from the etoricoxib development program.

Thrombotic CV safety data from the EDGE study are also presented, but separate from the existing pooled analysis as this study is prespecified to be included in a future pooled analysis of CV safety data from two additional studies which are currently ongoing (Section 8); EDGE II (Etoricoxib vs. Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness Trial in RA Patients), and MEDAL (Multinational Etoricoxib and Diclofenac Arthritis Long-term Study). The EDGE CV safety data do provide important additional information which reinforces the observations from the pooled analysis.

Pooled CV Phase IIb/III Analysis (Section 6.4.1)

The pooled analysis consists of final data from the etoricoxib chronic exposure studies, and includes over 6700 patients representing approximately 6500 patient-years at risk. In these studies, a total of 124 adverse experiences in 116 patients were adjudicated. Of these, 74 Confirmed Thrombotic CV serious adverse experiences occurred in 69 patients. Comparisons to naproxen were kept separate from comparisons with other nonselective NSAIDs based primarily on naproxen's pharmacodynamic effect, resulting in potent and sustained anti-platelet effects (>90% across its dosing interval) when dosed in the regimen used in these studies (500 mg twice daily) [6; 7]. A second reason for keeping the comparison to naproxen separate was the qualitative difference observed in the comparison of etoricoxib to naproxen vs. the comparison of etoricoxib to the other NSAIDs (ibuprofen and diclofenac combined). These differences were consistent with the hypothesis based on pharmacodynamic effects. Three data sets were thus defined in order to allow for the following comparisons: (1) Placebo-Controlled Data Set which compared etoricoxib to placebo, (2) Non-Naproxen-NSAID-Controlled Data Set which compared etoricoxib to all NSAID comparators pooled other than naproxen (diclofenac, ibuprofen), (3) Naproxen-Controlled Data Set which compared etoricoxib to naproxen. In all three data sets, the etoricoxib group consisted of combined data for all etoricoxib doses of 60 mg or greater.

When comparing etoricoxib either to placebo or to non-naproxen-NSAIDs, there was no evidence of a discernible difference in event rates. When comparing etoricoxib to naproxen, a lower event rate was observed with naproxen, suggesting a true difference in event rates is likely between these two groups. The difference between etoricoxib and naproxen begins shortly after initiation of therapy.

Overall, there was no clear pattern to the specific adverse experiences. In all three data sets, adverse experiences were generally reported in all 3 vascular beds, with more cardiac events than cerebrovascular or peripheral vascular events regardless of treatment group. In considering the difference between the naproxen and etoricoxib groups, no single type of adverse experience predominated, although a higher incidence of ischemic cerebrovascular stroke was observed with etoricoxib compared to naproxen.

Supportive Analyses

Antecedent Hypertension, Disease, and Dose

In order to further evaluate the thrombotic CV safety of etoricoxib, post-hoc subgroup analyses and analyses by dose were performed. One analysis evaluated whether there was a correlation between antecedent hypertension and CV events. Another analysis evaluated subgroups by disease, specifically looking at OA and RA patients. CV events were also evaluated by etoricoxib dose (60, 90, and 120 mg). In these analyses, relative risks were generally similar between the subgroups suggesting no correlation between these parameters and the risk of a confirmed thrombotic CV serious adverse experience.

CV Risk Factors

In order to further evaluate the thrombotic CV safety of etoricoxib, post-hoc subgroup analyses were performed. The main analysis included patients at increased CV risk at baseline, defined as having 2 or more of the 4 primary cardiac risk factors or a history of symptomatic atherosclerotic cardiovascular disease. For etoricoxib, these analyses were performed on the naproxen-controlled data set, since this is the largest data set. The difference observed in the total cohort between naproxen and etoricoxib was generally observed in both the increased-risk and the not-increased-risk patient subgroups. Treatment-by-subgroup interaction tests were not significant. Thus, available data provided no evidence of a different relative risk associated with etoricoxib versus naproxen for patients at increased CV risk in comparison to patients not at increased CV risk.

EDGE CV Data (Section 6.4.2)

The EDGE CV analysis included 7111 patients, representing approximately 5400 patient-years at risk. The prespecified primary endpoint for this analysis was Confirmed Thrombotic CV serious adverse experiences. The primary analysis was based on 68 confirmed thrombotic adverse experiences in 65 patients. Three patients had more than one adverse experience within the specified period, yielding a total of 65 patients with

confirmed thrombotic CV serious adverse experiences included in the analyses. There were 35 patients in the etoricoxib group and 30 in the diclofenac group with confirmed thrombotic CV serious adverse experiences, resulting in rates of 1.25 and 1.15 per 100 patient-years, respectively, with a relative risk of 1.07 (95% CI for the relative risk of 0.65, 1.74). Results for the APTC events were generally similar to those of Confirmed Thrombotic CV serious adverse experiences.

Evaluation of individual events indicated small numeric differences between treatments for certain event types; some occurring at a higher rate on etoricoxib and some occurring at a lower rate, as expected for two treatments with similar overall rates. Specifically, small numeric differences favoring etoricoxib were observed for confirmed ischemic cerebrovascular stroke, whereas small numeric differences favoring diclofenac were observed for confirmed acute myocardial infarctions. None of these differences was statistically significant. The absolute number of any of these individual events was small, and results at the level of individual events cannot be appropriately interpreted further.

Supportive Analyses

CV Risk Factors

In order to further evaluate the thrombotic CV safety of etoricoxib, post-hoc subgroup analyses were performed. Two subgroups previously defined for the pooled analysis were analyzed. Patients with an increased CV risk at baseline, defined the same as for the pooled analysis as patients having 2 or more primary cardiac risk factors or a history of symptomatic atherosclerotic cardiovascular disease. The other subgroup analysis performed was by aspirin use.

As expected, event rates were higher in the increased-risk subgroup for both treatments. However, consistent with the overall results, no difference was observed between etoricoxib and diclofenac in both the increased-risk and the not-increased-risk patient subgroups. Treatment-by-subgroup interaction tests were not significant, indicating no important departure from similarity of treatment effects across subgroups. Results for the aspirin use analysis were also consistent with the overall results, showing similar rates for etoricoxib and diclofenac in both the aspirin user and non-user subgroups.

Mortality (Section 7)

A total of 28 patients died in the etoricoxib development program, either while taking study medication, or within 14 days of discontinuing study medication, or as a result of a serious adverse experience that began within 14 days of discontinuing study drug. All deaths occurred in the chronic exposure studies; none occurred in Phase I/Clinical Pharmacology, Acute Analgesia, or Acute Gouty Arthritis studies.

All deaths were adjudicated by the Vascular Events Adjudication Committee to determine specific cause of death. The overall mortality rates per 100 patient-years were 0.30 for placebo, 0.49 for etoricoxib, 0.40 for non-naproxen NSAIDs, and 0.29 for

naproxen, with 95% CI's broadly overlapping among all the treatment groups. A review of these mortality rates, which factored in imbalances between exposure groups, provided no evidence of significant difference between treatment groups (etoricoxib, naproxen or non-naproxen NSAID) or by category of CV event.

Ongoing Studies to Further Assess Thrombotic CV Safety (Section 8)

In support of an ongoing assessment of the thrombotic CV safety profile of etoricoxib, 3 individual large, randomized, double-blind, active comparator-controlled, clinical studies were designed (EDGE, EDGE II, and MEDAL). The EDGE study is already complete, with CV safety results provided. Data from EDGE will be combined with data from EDGE II and MEDAL in a prespecified analysis of CV data from the 3 studies. The studies were designed with this primary objective in mind. Together, these studies represent the largest NSAID analysis ever designed (>34,500 patients) and include diclofenac as the active comparator for purposes of comparative CV safety. Diclofenac is an appropriate comparator as it represents the only NSAID which met all the key criteria established, as detailed in Section 8. Briefly, these include the fact that diclofenac is effective in the treatment of both OA and RA, it is used extensively worldwide, it lacks potent and sustained antiplatelet activity, it has no pharmacodynamic interaction with aspirin, its effects on blood pressure are generally considered modest, and it can be dosed twice daily for patient convenience. MEDAL, as well as EDGE and EDGE II, are generating CV safety data in two large and common patient populations intended for treatment, namely patients with OA or RA. The specific OA and RA patient populations being studied include patients with a range of CV risk, and aspirin users and nonusers. MEDAL alone includes approximately 23,500 patients with OA and RA. EDGE II includes over 4000 RA patients, again with a range of CV risk and both aspirin users and nonusers. These studies will provide information to assess effect of dose (etoricoxib 60 mg and 90 mg included) and disease (OA versus RA). MEDAL, as well as EDGE II, will provide an extensive amount of long term (>18 months) CV safety data comparing a selective COX-2 inhibitor and a nonselective NSAID without potent and sustained antiplatelet effects in patients who require chronic anti-inflammatory therapy.

DISCUSSION

Etoricoxib, a selective COX-2 inhibitor, was developed to diversify the existing armamentarium of medications for the treatment of inflammatory conditions as well as acute pain and chronically painful conditions. The efficacy of etoricoxib has been demonstrated in the treatment of acute gouty arthritis, one of the most intense inflammatory conditions known. This along with its efficacy in AS and its efficacy in the treatment of OA, RA, CLBP, and a variety of acute pain models highlights the broad clinical utility of etoricoxib.

Etoricoxib has established a GI safety and tolerability profile superior to nonselective NSAIDs, consistent with the proven benefit of selective COX-2 inhibition. In a

comprehensive GI safety program, GI safety was demonstrated by a significant decrease in fecal red blood cell loss versus ibuprofen, a decrease in endoscopic ulcers versus ibuprofen and naproxen, and a decreased rate of PUBs (PUB results driven primarily by the comparison to naproxen). In addition, a significant improvement in GI tolerability was demonstrated with etoricoxib; versus NSAIDs in a prespecified pooled analysis of data across the clinical development program, and versus diclofenac in the EDGE study.

With regard to renovascular safety, etoricoxib, at doses recommended for chronic use (60 mg and 90 mg), and extending up to the dose recommended for acute pain and acute gouty arthritis (120 mg), manifests effects on blood pressure that are generally similar to NSAIDs, with numeric differences in some studies favoring etoricoxib compared with ibuprofen, and in some but not all studies favoring naproxen. In the EDGE study a difference was observed favoring diclofenac, likely related to the 90-mg dose of etoricoxib evaluated in that study. Not unexpectedly, due to the known mechanism of action, there is evidence for a dose-related trend in hypertension-related adverse experiences, albeit shallow.

The issue of CV safety has become an important consideration in the overall safety profile of selective COX-2 inhibitors. Based on tabulations of thrombotic CV serious adverse experiences from studies of at least 4 weeks in duration and adjudicated by expert committees blinded to the data, there is no discernible difference in event rates among patients taking etoricoxib, placebo, or NSAIDs which lack potent and sustained antiplatelet activity. Naproxen is associated with an incidence of thrombotic CV serious adverse experiences which is lower than that observed with etoricoxib. When viewed in the context of the cardiovascular safety data of etoricoxib vs. placebo and vs. non-naproxen-NSAIDs and taking into consideration the pharmacodynamic effects of the specific and regimented dosing of naproxen used in these studies (500 mg twice daily), this observation is consistent with naproxen's potent and sustained antiplatelet effects. The weight of evidence supporting an antiplatelet effect for naproxen is based on pharmacodynamic data as well clinical data with other NSAIDs with potent and sustained antiplatelet activity (indobufen, flurbiprofen). Furthermore, the observations from the etoricoxib clinical development program are not inconsistent with recently published data on a GI outcomes study (TARGET) evaluating lumiracoxib, ibuprofen, and naproxen in approximately 18,000 patients with OA [8]. TARGET consisted of 2 substudies of equal size with one comparing lumiracoxib to ibuprofen 800 mg 3x daily and the other lumiracoxib to naproxen 500 mg 2x daily. In TARGET, the hazard ratio (95% CI) of confirmed or probable APTC events for lumiracoxib versus ibuprofen was 0.76 (0.41, 1.40) while the hazard ratio (95% CI) of confirmed or probable vascular APTC for lumiracoxib versus naproxen was 1.46 (0.89, 2.37). The differences between lumiracoxib and ibuprofen and between lumiracoxib and naproxen were not significant (p=0.3775 and p=0.1313, respectively), and the treatment-by-substudy interaction result was nonsignificant (p=0.1145). However, the TARGET study was not powered for the

cardiovascular endpoint. The hazard ratio for the APTC combined endpoint in the lumiracoxib versus naproxen substudy is not inconsistent with the hypothesis that naproxen 500 mg twice daily has cardiovascular effects different from ibuprofen and lumiracoxib.

Recent events have further increased attention on thrombotic cardiovascular safety. In the rofecoxib Adenomatous Polyp PREvention On VIOXX™ (APPROVe) study, the risk of sustaining a thrombotic CV event for the rofecoxib group (25 mg once daily) began to diverge from placebo beginning after 18 months of chronic therapy; over time the difference became significant. The mechanism(s) of the CV safety findings in APPROVe were uncertain and at the time several hypotheses were proposed to explain the APPROVe findings. These included hypotheses based on molecule specific effects unrelated to the inhibition of COX-2, inhibition of COX-2 which proposed that all NSAIDs could increase the risk of thrombotic cardiovascular events versus placebo, and hypotheses based on an imbalance in inhibition of COX-2 versus COX-1 which proposed that selective COX-2 inhibitors and not non-selective NSAIDs would increase the risk. With regard to molecule specific effects, one study suggested a pro-oxidant effect associated with sulfone-containing moieties due to sulfone-mediated oxidation of LDL, and that molecules with a sulfonamide moiety such as celecoxib and valdecoxib would not have this effect [9]. Recent revelations regarding the increased cardiovascular risk of celecoxib and valdecoxib would appear to make molecule-specific arguments such as this untenable. There were also hypotheses proposing that differences among agents in their propensity to affect blood pressure were the basis for the findings; however, extensive analyses of the rofecoxib data base do not support this association, including the APPROVe data in which the increased risk of thrombotic cardiovascular events observed was greater than would be predicted by the observed changes in blood pressure. Additional hypotheses suggested that selective COX-2 inhibition may promote atherosclerosis [10; 11; 12].

Shortly after the APPROVe data were announced, data were released from a study in which the perioperative administration of valdecoxib and parecoxib increased the risk of cardiovascular events in patients who had undergone coronary artery bypass grafting surgery [13]. Results from this study confirmed observations from a smaller study published previously [14]. It has also been announced publicly that celecoxib 400 and 800 mg daily increased the risk of thrombotic CV events compared to placebo in one colon polyps prevention trial, but that an increased risk was not observed with celecoxib 400 mg in another colon polyps trial [15]. It was also recently announced that patients in an Alzheimer's Disease prevention study taking naproxen sodium 220 mg twice daily, but not patients taking celecoxib 200 mg twice daily, had a numeric increase in thrombotic cardiovascular events compared to patients taking placebo [16].

Other than COX-2 selective inhibitors, aspirin is the only NSAID with long term safety data. Although the data noted above suggest the cardiovascular safety findings may

represent a class effect, it is unclear at this time how extensive the class is: selective COX-2 inhibitors, all NSAIDs, or the subset of NSAIDs without potent and sustained COX-1 inhibitory effects.

In response to data that have become available since late September 2004, Merck proactively revised the etoricoxib core label for those countries in which the drug has been approved to reflect the current state of knowledge. Prior to this revision, the label already included a precaution for patients with a medical history of ischemic heart disease. The revised label for countries in which etoricoxib is marketed now includes the following information: CV safety results from the etoricoxib EDGE study, results from the rofecoxib APPROVe study, and results of the parecoxib/valdecoxib study in patients following coronary artery bypass grafting. A recommendation against the use of etoricoxib by patients who have recently undergone coronary artery bypass graft surgery or angioplasty or in patients with acute coronary syndrome is also included. These revisions have been distributed to all markets where etoricoxib is currently licensed.

Limitations on the existing etoricoxib cardiovascular safety data include the duration of the placebo-controlled data (up to 12 weeks in duration) and the amount of longer term data. However, in the near future, a tremendous amount of data, including long term exposure, will be forthcoming from ongoing outcomes studies with etoricoxib. The MEDAL study was specifically designed and powered to further assess CV risk in a patient population (OA and RA patients) intended for the use of COX-inhibiting agents. These CV data will firmly establish the CV safety profile of etoricoxib relative to the non-selective NSAID diclofenac, an NSAID which is used worldwide for symptomatic benefit in arthritis sufferers and is considered a safe and effective treatment.

CONCLUSIONS

- The data as summarized above have resulted in etoricoxib's approval worldwide in 60 countries and are under review by the FDA.
- Etoricoxib has demonstrated efficacy in the treatment of OA, RA, AS, CBLP, acute gouty arthritis, and acute pain including primary dysmenorrhea; and has demonstrated anti-inflammatory properties that are comparable and in some cases, superior to nonselective NSAIDs.
- Etoricoxib has a substantially improved GI safety profile compared with nonselective NSAIDs. In 2 large endoscopy studies, etoricoxib 120 mg is associated with an incidence of endoscopic ulcers significantly lower than ibuprofen and naproxen, but greater than placebo. Analysis of all upper GI clinical events demonstrates that etoricoxib use is associated with a consistently lower incidence of upper GI clinical events than nonselective NSAIDs, with the results driven by comparisons to naproxen.

- The GI tolerability profile of etoricoxib is superior to that of nonselective NSAIDs, as evidenced by significantly lower new use of gastroprotective agents and significantly fewer discontinuations due to digestive system adverse experiences with etoricoxib than with nonselective NSAIDs. Superior GI tolerability was also established versus diclofenac in the EDGE study.
- Etoricoxib, at doses recommended for chronic use (60 mg and 90 mg) and extending up to the dose recommended for acute pain and acute gouty arthritis (120 mg), manifests effects on blood pressure that are greater than those of placebo but generally similar to those of NSAIDs.
- The incidence of edema-related adverse experiences with etoricoxib is low and generally of minimal consequence during chronic use at doses up to 120 mg daily and remains low after more than 1 year of therapy. The effects of etoricoxib on edema and body weight are generally similar to comparator NSAIDs.
- Data on thrombotic CV serious adverse experiences in the etoricoxib development program are limited by the duration of the placebo-controlled data (up to 12 weeks in duration) and the quantity of the long-term active comparator-controlled data. In analyses of thrombotic CV serious adverse experiences, including data from the EDGE study, there is no evidence of a discernible difference in event rates among patients taking etoricoxib, placebo, or non-naproxen NSAIDs. Naproxen 500 mg twice daily, however, is associated with a lower incidence of thrombotic CV serious adverse experiences than etoricoxib. The difference begins shortly after initiation of therapy.
- Revised labeling, which already includes a precaution for patients with a medical history of ischemic heart disease, has been distributed to countries in which etoricoxib is marketed and now includes information on the CV safety results from the etoricoxib EDGE study, results from the rofecoxib APPROVe study, and results of the parecoxib/valdecoxib study in patients following coronary artery bypass grafting. A recommendation against the use of etoricoxib by patients who have recently undergone coronary artery bypass graft surgery or angioplasty or in patients with acute coronary syndrome is also included.
- Appropriately designed studies are currently ongoing to further assess the CV safety of etoricoxib in patients who require treatment with NSAIDs or selective COX-2 inhibitors.

1. Introduction

Etoricoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, was developed to provide analgesic and anti-inflammatory effects similar to nonselective cyclooxygenase (COX-1/COX-2) inhibitors commonly known as nonsteroidal anti-inflammatory drugs (NSAIDs) and with an improved gastrointestinal (GI) safety profile consistent with the benefit that has been established with selective COX-2 inhibition [17]. Etoricoxib is currently approved in 60 countries worldwide. The core therapeutic indications for etoricoxib in countries where etoricoxib is approved are osteoarthritis (OA) (60 mg once daily), rheumatoid arthritis (RA) (90 mg once daily), and acute gouty arthritis (120 mg once daily for the acute symptomatic period). In certain countries, indications are also approved for acute pain (120 mg once daily for the acute symptomatic period), primary dysmenorrhea (120 mg once daily for the acute symptomatic period) and chronic low back pain (CLBP) (60 mg once daily). In the United States, a New Drug Application (NDA) for etoricoxib is under review by the Food and Drug Administration (FDA), with an approvable letter received in October 2004.

The purpose of this document is to provide a summary of the existing clinical data for etoricoxib. The focus of this summary is on two items: (1) the safety data from the clinical development program, with particular focus on key safety areas of interest: GI, renovascular, and thrombotic cardiovascular (CV) safety; (2) a review of the ongoing etoricoxib studies designed to further assess the CV safety profile of etoricoxib.

1.1 Organization of the Document

Following a brief review of clinical pharmacology and efficacy (Sections 2 and 3) the clinical safety profile of etoricoxib is presented in this document, with a main focus on GI, renovascular, and CV safety. The document is organized such that analyses of GI safety (Section 4) are first presented, followed by a review of renovascular safety (Section 5), and then CV safety (Section 6), including information on Postmarketing CV data (Section 6.5), and a summary of mortality for the clinical program (Section 7). Following the safety summary is a section devoted to a description of the ongoing studies designed to further assess the CV safety profile of etoricoxib (Section 8).

The general safety profile of etoricoxib is based primarily on data from 4087 patients treated with etoricoxib across 13 Phase IIb/III studies in OA, RA, AS, and CLBP. These 13 studies are collectively referred to as the Chronic Exposure Studies because they are all studies in which study therapy was administered over an extended period of time—a minimum of 12 weeks with the majority of studies lasting greater than 52 weeks. This data set specifically consists of 5 OA studies, 3 RA studies, 2 CLBP studies, 1 AS study, and 2 upper GI endoscopy studies. To provide a comprehensive safety assessment, data from the Chronic Exposure Studies were analyzed and presented using populations and data sets that were defined by the comparator (placebo or active comparator) and duration of exposure (i.e., 12 weeks and 1 year). An additional 244 patients were treated with etoricoxib in a Phase III non-IND OA study (Protocol 805), in which diclofenac was the

active comparator. Data from this 6 week study were included in the GI safety (PUB) and CV analyses for completeness, but were not included in the general safety and tolerability summaries, including renovascular safety. Figure 1 is a diagrammatic summary of the Chronic Exposure Studies, and includes Protocol 805.

Two populations were chosen for the presentation of renovascular safety: the Placebo-Controlled Population (comprised of data from placebo-controlled periods from all Chronic Exposure Studies) and the 1-Year Continuous Exposure, Active-Comparator-Controlled Population (comprised of data over a continuous, 52-week treatment period from the 7 Chronic Exposure Studies which extended at least 1 year in duration). Respectively, these populations were designed to evaluate the safety of etoricoxib compared with placebo and the longer-term safety of etoricoxib compared with approved and commonly used nonselective NSAID therapies. Renovascular data in the form of clinical adverse experiences, body weight, and mean changes in blood pressure are reviewed for these two populations. To enhance the clinical review, statistical analyses were performed for both populations and descriptive statistics are presented.

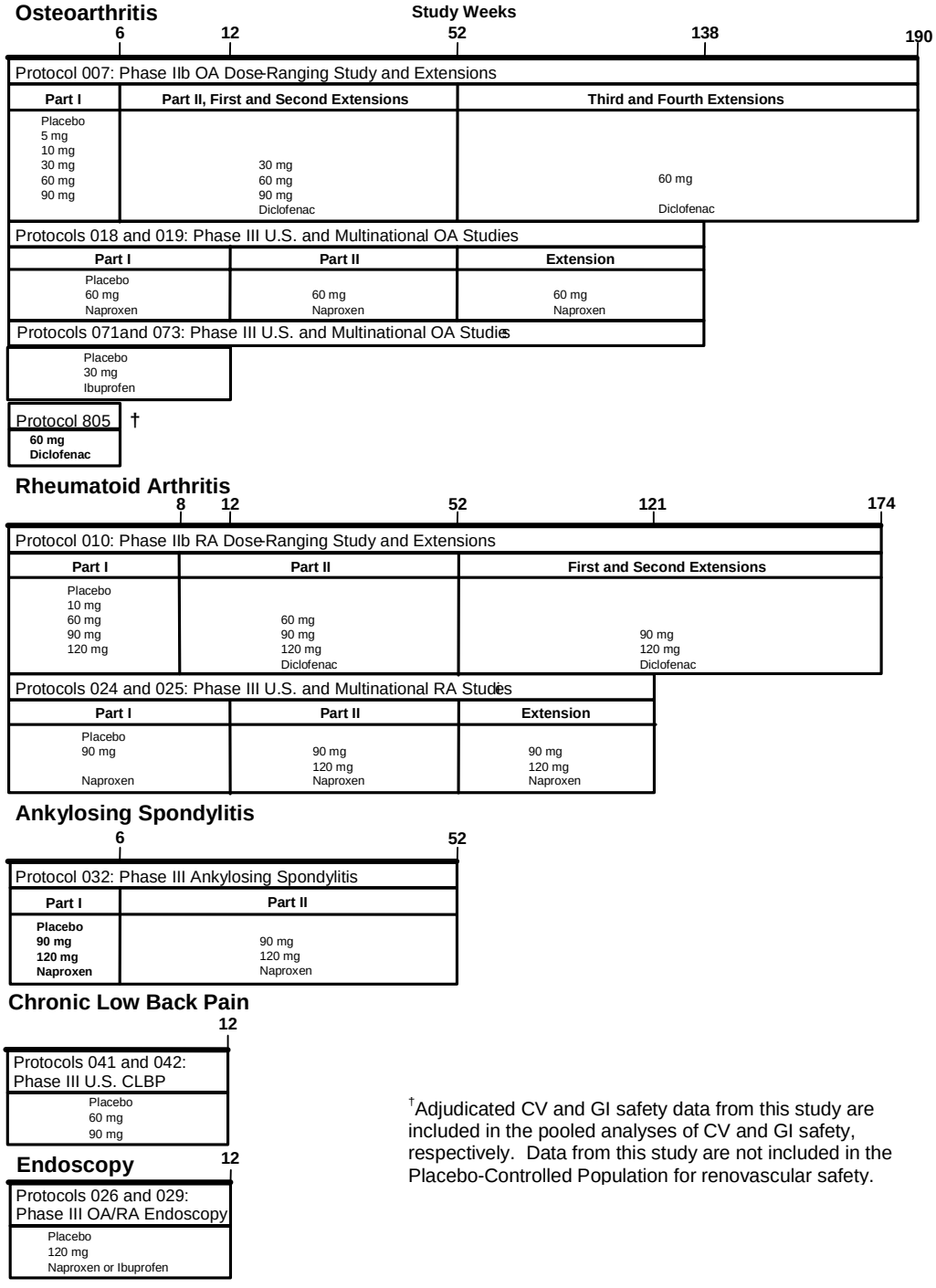
The data from the Chronic Exposure Studies were also combined for prespecified pooled analyses of GI (Section 4) and CV safety (Section 6) in order to increase precision. The data sets used for these analyses were defined by comparator NSAID and placebo use. They include studies with doses of etoricoxib $\geq$60 mg and therefore do not include Protocols 071 and 073, as these studies evaluated a dose of etoricoxib (30 mg) which had not yet been proven to be fully efficacious at the time the Adjudication Standard Operating Procedures (SOP) for GI and CV safety were written. Data for the GI safety and tolerability analyses were separated into Placebo-Controlled and Active-Comparator-Controlled data sets. Data for the thrombotic CV event analyses were similarly grouped into Placebo-Controlled and Active-Comparator-Controlled data sets; however, the Active-Comparator-Controlled data set was further divided into two groups, the Non-Naproxen-NSAID Controlled and Naproxen-Controlled data sets. These two data sets were specifically established due to pharmacodynamic difference among some nonselective NSAIDs, namely the differing antiplatelet effects that were observed for naproxen versus other nonselective NSAIDs such as ibuprofen and diclofenac [6; 7].

An additional study, EDGE, was performed to assess the GI tolerability of etoricoxib 90 mg versus diclofenac 150 mg in 7111 OA patients. This study was not integrated with the Chronic Exposure Studies because the EDGE study was much larger than the other studies and, as such, could provide an independent assessment of GI tolerability and general safety/tolerability of etoricoxib in comparison to the NSAID diclofenac. The CV safety data from EDGE are prespecified to be included in a future pooled analysis of CV safety data from two additional studies which are currently ongoing; EDGE II and MEDAL.

In total, 9954 subjects/patients were treated with etoricoxib in Phase I, II, and III studies, including the EDGE study. An additional 244 patients were treated with etoricoxib for 6 weeks in the non-IND OA study Protocol 805. Approximately 4672 patients received etoricoxib for longer than 6 months (at doses ranging from 30 to 120 mg).

Figure 1

Summary of Etoricoxib Studies Designated as Chronic Exposure Studies



†Adjudicated CV and GI safety data from this study are included in the pooled analyses of CV and GI safety, respectively. Data from this study are not included in the Placebo-Controlled Population for renovascular safety.

1.2 Collection of Data

Through the etoricoxib development program, the standard data collection for all adverse experiences included patients on drug and extending to 14 days after last dose of study therapy. In addition to this standard collection of information, all-patients-treated mortality data is provided for the EDGE study which was specifically prespecified to follow patients until the study ended. Therefore, all analyses described follow this standard unless otherwise specified.

2. Clinical Pharmacology

Etoricoxib has a dipyridine structure unique from other selective COX-2 inhibitors, and with a sulfone side chain. COX-2 selectivity has been demonstrated in vitro and demonstrated in human ex vivo whole blood assays within the clinical dose range [18; 19]. It is rapidly and completely absorbed following oral administration with a time to peak plasma concentration (T_{max}) occurring at approximately 1 hour and an absolute bioavailability of 100%. These properties likely contribute to etoricoxib's rapid onset of action. Etoricoxib displays linear pharmacokinetics up to at least twice the highest recommended dose of 120 mg [20]. Its effective half-life of ~22 hours supports its recommended once daily dosing. Elimination of etoricoxib is primarily through metabolism, with <1% of an administered dose recovered intact in urine [21]. The metabolism for etoricoxib is largely hepatic, with CYP3A playing an important role, but multiple other CYP isozymes are also involved [22].

3. Efficacy

This section provides a high level review of efficacy data in OA, RA, AS, CLBP, as well as acute gouty arthritis and models of acute pain (postdental surgery pain, postorthopedic surgery pain, and primary dysmenorrhea).

3.1 Efficacy of Etoricoxib in OA

The efficacy of etoricoxib in OA was demonstrated in 4 Phase III OA Studies: two 30-mg studies and two 60-mg studies. The 30 mg studies were 12-weeks in duration and compared etoricoxib 30 mg with placebo and ibuprofen 2400 mg. The 60 mg studies were 52-week base studies which compared etoricoxib 60 mg with placebo and naproxen 1000 mg. Although the etoricoxib 60-mg dose was found to be the minimal dose to provide maximal efficacy in the single OA Phase IIb dose-range-finding study [23], and thus studied in replicate Phase III studies, the 30-mg dose was evaluated in an attempt to establish the lowest effective etoricoxib dose in OA.

The efficacy of etoricoxib 30 mg and 60 mg was demonstrated by statistically significant ($p<0.001$) improvements compared with placebo, on all 3 primary endpoints (the WOMAC Pain Subscale, the WOMAC Physical Function subscale, and the Patient Global Assessment of Disease Status). Prespecified comparability was demonstrated between etoricoxib 30 mg and ibuprofen 2400 mg and between etoricoxib 60 mg and naproxen 1000 mg [24; 25] (manuscript in progress).

3.2 Efficacy of Etoricoxib in RA

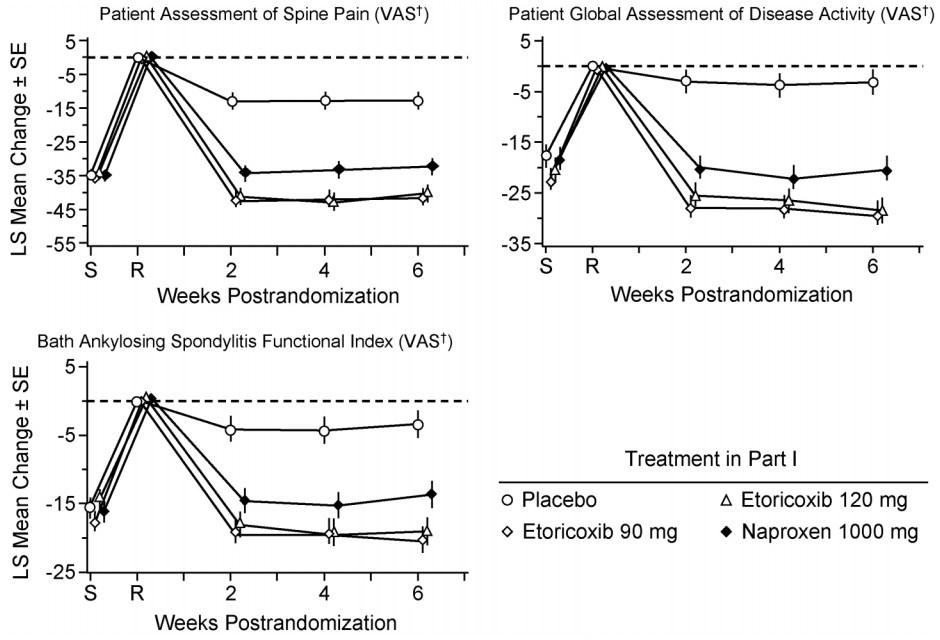
The efficacy of etoricoxib in RA was demonstrated in 2 Phase III studies, comparing etoricoxib 90 mg with placebo and naproxen 1000 mg [26; 27]. The efficacy of etoricoxib 90 mg was demonstrated by significant ($p<0.050$) improvements compared with placebo, on all 4 primary endpoints (Tender Joint Count, Swollen Joint Count, and Patient and Investigator Global Assessments of Disease Activity). In addition, the efficacy of etoricoxib was significantly superior to naproxen in one study ($p\leq0.05$ for all primary endpoints) and similar to naproxen in a second study. Consistent with the results observed with the primary endpoints, patients on etoricoxib 90 mg demonstrated significantly ($p<0.001$) greater improvement in ACR20 when compared with those on placebo; when compared to naproxen, the percent of ACR20 responders on etoricoxib 90 mg was higher in one study and generally similar to naproxen in the second study.

3.3 Efficacy of Etoricoxib in AS

The efficacy of etoricoxib in AS was demonstrated in one Phase III, 52-week study, comparing etoricoxib 90 mg and 120 mg with placebo and naproxen over a 6-week placebo period (Part I), followed by a 46-week active-comparator-controlled period (Part II) [28]. The efficacy of etoricoxib in AS was demonstrated by significantly ($p<0.001$) greater mean improvements compared with placebo on all 3 primary endpoints over the 6-week treatment period (Patient Assessment of Spine Pain, Bath Ankylosing Spondylitis Functional Index, and Patient Global Assessment of Disease Activity). Results for etoricoxib 90 mg and 120 mg were generally similar, with significantly ($p<0.05$) greater improvements compared with naproxen on all 3 primary endpoints (Figure 2). The study also demonstrated the durability of effect of etoricoxib 90 mg and 120 mg in AS over the course of 52 weeks with the superiority of etoricoxib to naproxen maintained over time for all 3 primary endpoints ($p<0.05$).

Figure 2

Primary Endpoints: LS Mean Change From Baseline
Over the 6-Week Treatment Period (Part I)
Phase III AS Study



† 0- to 100-mm scale.
S=Screening visit; R=Randomization (Baseline) visit; SE=Standard error; LS=Least Squares; S to R=Washout period for prior AS therapy.

3.4 Efficacy of Etoricoxib in Chronic Low Back Pain (CLBP)

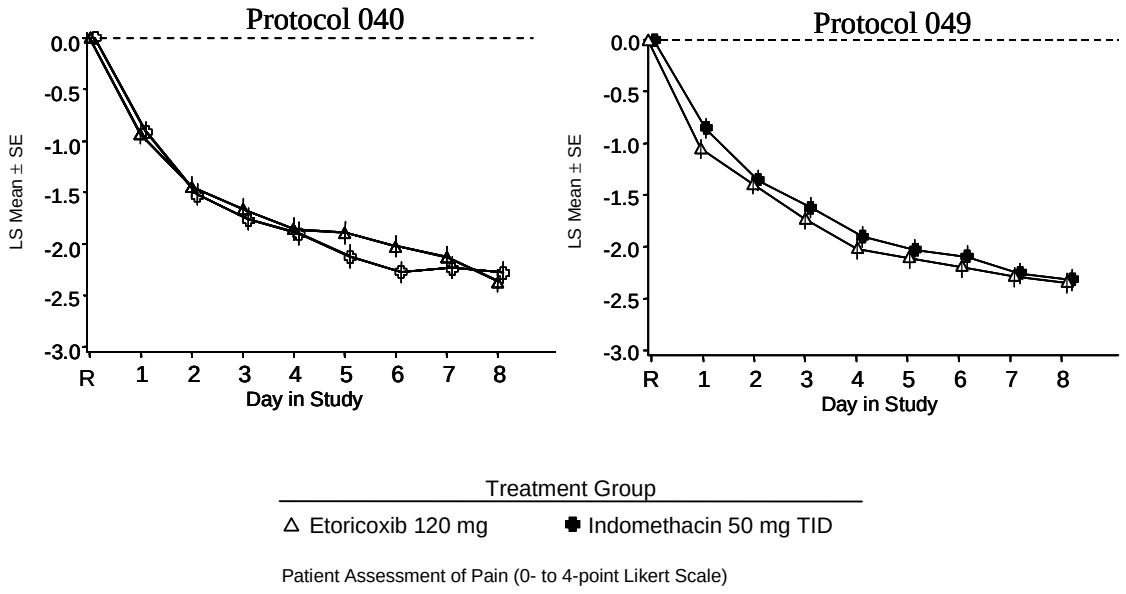
The efficacy of etoricoxib in CLBP was demonstrated in two Phase III, 12-week studies [29; 30]. Patients receiving etoricoxib 60 or 90 mg reported significantly ($p<0.001$) less pain based on the primary endpoint (Low Back Pain Intensity Scale) than those receiving placebo in each study over the first 4 weeks of the treatment period (specified as the primary assessment period) and over the entire 12-week treatment period (secondary assessment period). The treatment responses to etoricoxib 60 and 90 mg were similar. A significant improvement was evident after 7 days of treatment, the first assessment following randomization and the treatment effects were maintained throughout the entire 12-week treatment period.

3.5 Efficacy of Etoricoxib in Acute Gouty Arthritis

The efficacy of etoricoxib in acute gouty arthritis was demonstrated in 2 Phase III studies, comparing etoricoxib 120 mg once daily with indomethacin 50 mg 3 times daily [31; 32]. Comparable efficacy between etoricoxib and indomethacin was demonstrated based on prespecified comparability bounds. These data showed that etoricoxib 120 mg administered once daily is efficacious, with clinical efficacy comparable to indomethacin 50 mg administered 3 times daily, for the treatment of acute gouty arthritis. Results from both studies are shown in Figure 3. These data and the study design were presented and discussed at an FDA advisory panel meeting on June 2 and 3, 2004.

Figure 3

Primary Endpoint: Patient's Assessment of Pain
LS Mean Change From Baseline: Days 2 to 8
Phase III Acute Gouty Arthritis Studies



R=Randomization (Baseline) visit; SE=Standard error; LS=Least squares; TID=3 times a day.

3.6 Efficacy of Etoricoxib in Acute Analgesia

Acute analgesia studies were carried out including postdental surgery, primary dysmenorrhea, and postorthopedic surgery. The efficacy of etoricoxib 120 mg was demonstrated in all three models, with etoricoxib 120 mg demonstrating an overall analgesic effect that was significantly or numerically greater than placebo. In addition, the analgesic effect of etoricoxib 120 mg was demonstrated to be generally similar to that of naproxen sodium (550 mg) and ibuprofen (400 mg), and superior to acetaminophen/codeine 600/60 mg and oxycodone/acetaminophen 10/650 mg [33; 34; 35; 36; 37].

Data from the acute analgesia clinical program showed that etoricoxib demonstrated effects that were generally similar to non-selective NSAIDs, significantly greater than placebo, and similar to or greater than short-acting oral opioids.

3.7 Efficacy Conclusions

The efficacy of etoricoxib has been demonstrated in a range of diseases and conditions.

- Etoricoxib has demonstrated potent anti-inflammatory properties that are comparable and in some cases, superior to nonselective NSAIDs.
    - Clinical efficacy superior to naproxen was demonstrated in AS over a 52-week treatment period and in 1 of 2 RA studies over a 12-week period.
    - Clinical efficacy comparable to indomethacin (150 mg) was demonstrated in 2 of 2 acute gouty arthritis studies.

4. GI Safety and Tolerability

4.1 Organization of Section

This section summarizes the etoricoxib GI safety data, which provide evidence of an improved GI safety profile versus non-selective NSAIDs.

The etoricoxib GI safety program was comprehensive and included studies of gastric mucosal prostaglandin synthesis, fecal blood loss, surveillance endoscopy and prespecified analyses of clinical upper GI events (gastroduodenal perforations, symptomatic gastroduodenal ulcers, and upper GI bleeds, [PUBs]) and GI tolerability. For brevity, selected data are summarized, beginning with data regarding cumulative rates of endoscopic ulcers found in surveillance endoscopy studies. Data regarding the incidence of PUBs are presented next from a pooled analysis of the active comparator-controlled portions of Phase IIb/III studies. PUB data are also reported from the EDGE study. Of note, the PUB data from the EDGE study were tabulated for completeness, but PUBs were not a prespecified hypothesis tested endpoint in this study due to the fact that the rates of PUBs were confounded by both aspirin and liberal gastroprotective agent (GPA) use (~18% of patients). Data regarding the primary endpoint of GI tolerability in EDGE are also presented as are data from the prespecified analysis of GI tolerability.

4.2 GI Adjudication Standard Operating Procedure (SOP)

A rigorous adjudication of all potential clinical upper GI events was accomplished through the establishment of a GI Adjudication SOP which mandated that all cases of suspected clinical upper GI perforations, gastroduodenal ulcers, or bleeds (PUBs) from all studies containing any dose of etoricoxib be submitted to an external expert, independent, blinded Case Review Committee (CRC). Blinded investigators monitored clinical trials for suspected PUBs. If, in the judgment of the investigator, a PUB occurred, medical records were sent to the CRC for review. The expert panel, which was also blinded to treatment, used prespecified criteria to determine whether events were confirmed, and whether they were clinically complicated. All adjudication decisions by the committee were final.

4.3 Definition of Adjudicated Endpoints

The definition of PUB endpoints that were used by the blinded, independent, expert CRC included the following:

1. Confirmed PUBs
2. Confirmed plus unconfirmed PUBs (all investigator reported PUBs)
3. Confirmed complicated PUBs (a subset of confirmed PUBs, defined as complicated according to a set of prespecified criteria)
4. Confirmed plus unconfirmed complicated PUBs (a subset of # 2)

A complicated PUB was defined as a gastroduodenal perforation, gastric outlet obstruction due to an ulcer, or a major upper GI bleed (as defined by clinical and laboratory evidence of large volume blood loss, such as orthostatic changes in vital signs, need for transfusion of blood products, decrease in hemoglobin $\geq$2 gm/dL, or other evidence of significantly reduced circulatory volume).

A PUB event was considered confirmed if it was confirmed by the independent CRC according to prespecified criteria which also allowed the CRC to determine if the event was clinically complicated or not [38]; the specific final diagnosis (e.g., gastric or duodenal ulcer, GI bleeding event, etc.) was assigned by the CRC. The CRC could also classify a potential event as not an upper GI event.

4.4 Upper GI Safety Results

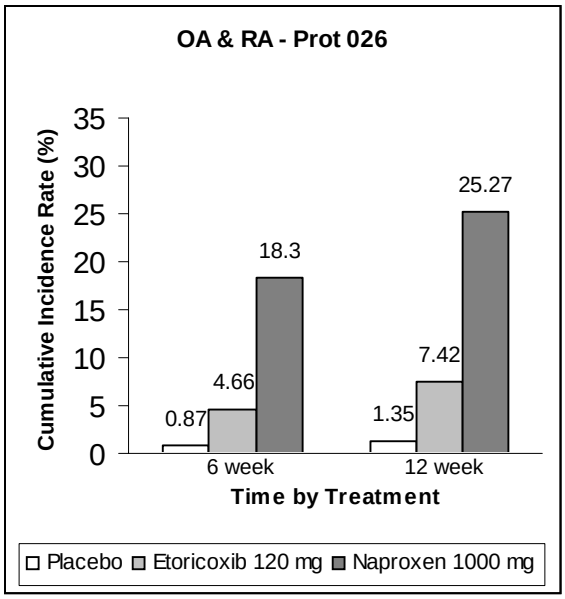
The upper GI safety assessment of etoricoxib focused on both rates of endoscopic ulcers as well as on the collection, prospective adjudication and analysis of PUBs. Two endoscopy studies analyzed the difference in cumulative incidence of ulcers ($\geq$3 mm gastroduodenal ulcers) over 12 weeks in OA and RA patients between etoricoxib, placebo and the non-selective NSAIDs (ibuprofen or naproxen). The PUB analyses were based on data from all Phase IIb/III studies with duration of greater than 4 weeks from the clinical development program, referred to previously as the chronic exposure studies.

4.4.1 Endoscopy Studies in OA and RA Patients

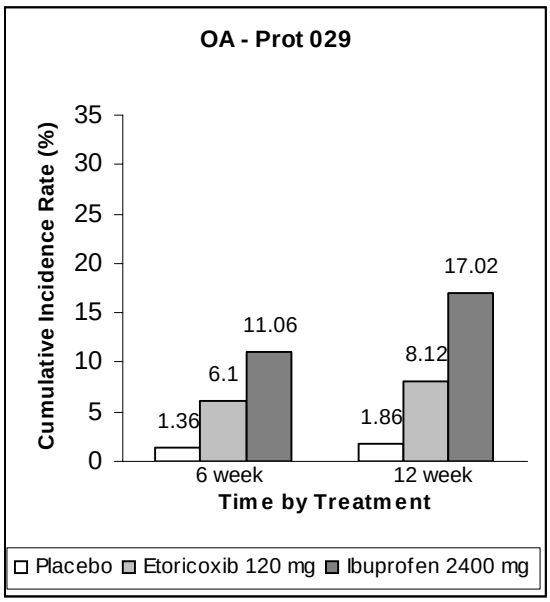
Two endoscopy studies were carried out to assess cumulative rates by 12 weeks of endoscopic ulcers (≥3 mm) in patients taking etoricoxib 120 mg (the maximal recommended dose and 30-60 mg more than the maximal recommended doses for chronic use), placebo or ibuprofen 2400 mg daily in OA patients (Protocol 029) or in patients taking etoricoxib 120 mg, placebo or naproxen 1000 mg daily in OA and RA patients (Protocol 026) (Figure 4) [39; 40]. In both studies, the incidence of ulcers (≥3 mm) by 12 weeks in the etoricoxib groups were significantly lower than the corresponding incidence for the individual non-selective NSAIDs. In both studies, etoricoxib 120 mg showed a higher incidence of ulcers than placebo by 12 weeks.

Figure 4

Cumulative Incidence Rate of Gastroduodenal Ulcers (≥3 mm)
Endoscopy Studies



For cumulative incidence over 12 weeks:
p<0.001 etoricoxib vs. naproxen
p=0.002 etoricoxib vs. placebo



For cumulative incidence over 12 weeks:
p<0.001 etoricoxib vs. ibuprofen
p<0.003 etoricoxib vs. placebo

4.4.2 Pooled Analyses of PUBs and GI Tolerability

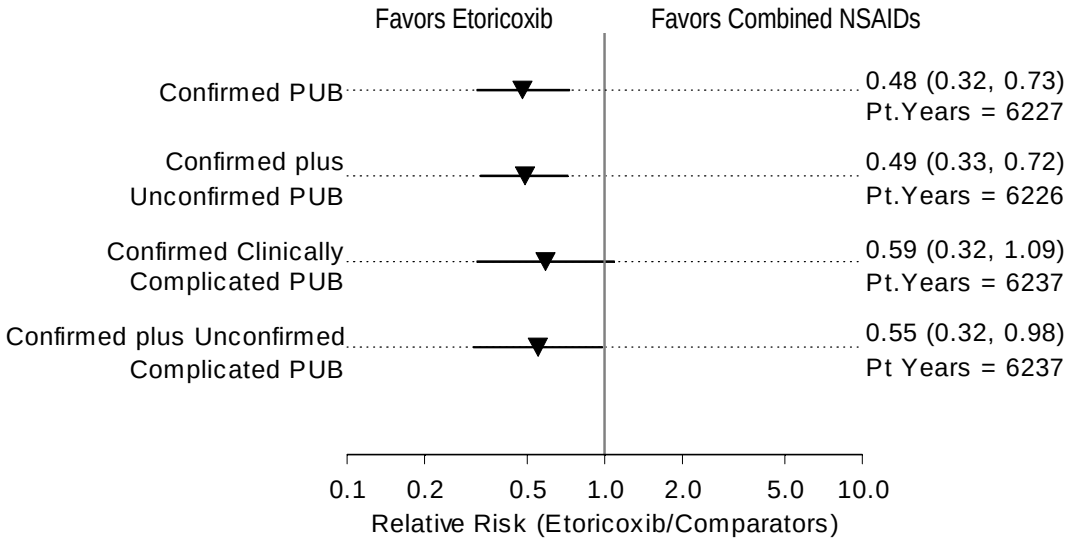
Pooled Analysis of PUBs

A pooled analysis of PUBs was performed in patients from the chronic exposure studies. Adjudicated PUBs from unscheduled endoscopies in the two endoscopy studies were included (ulcers found at scheduled surveillance endoscopies were excluded from this analysis.) The analysis includes data from a total of 5441 patients (Figure 5) [40].

In this analysis, there was a statistically significant ($p \leq 0.001$) 52% reduction in the relative risk of confirmed PUBs with etoricoxib (all doses ≥60 mg combined) versus non-selective NSAIDs combined. The rate per 100 patient-years for the confirmed PUB endpoint over the entire follow up period was 1.00 for the etoricoxib group versus 2.47 for the combined NSAIDs group (relative risk [95% Confidence Interval (CI)] of 0.48 [0.32, 0.73]). Results for the other 3 PUB endpoints were consistent with these results. The results in the nonselective NSAID group were driven mainly by naproxen; the data for the other NSAIDs (diclofenac, ibuprofen) individually were limited.

Figure 5

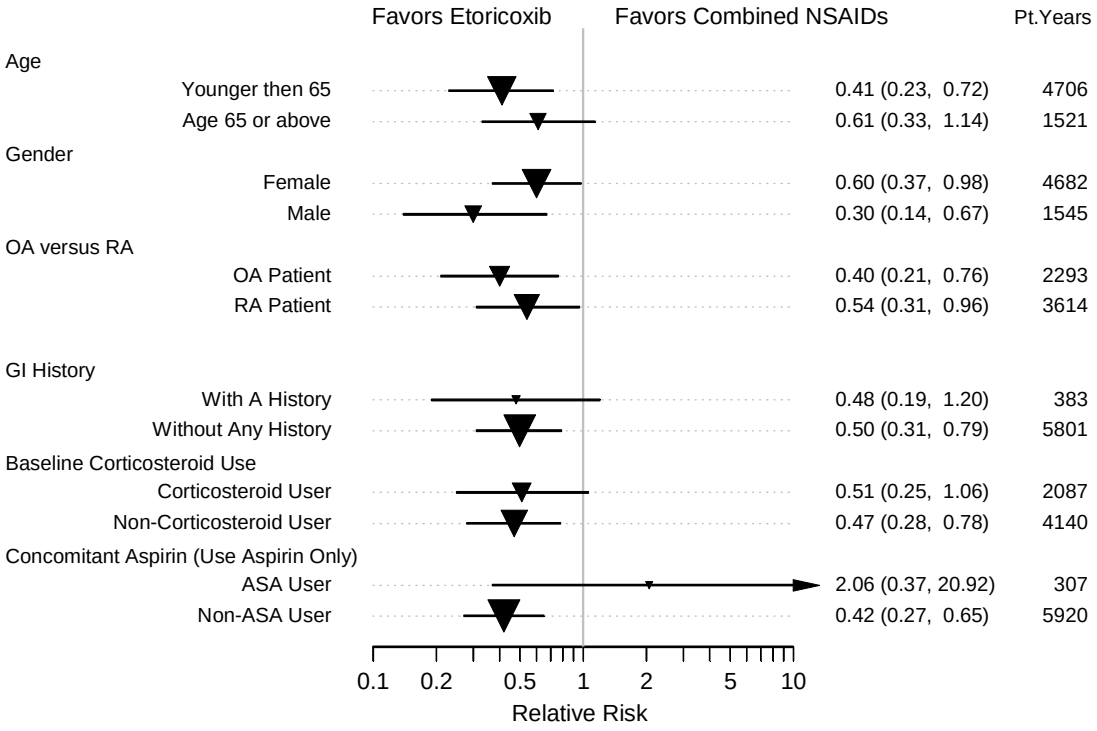
Relative Risk (95% CIs)
Pooled Analysis of PUBs Over Entire Study Duration



Subgroup analyses of PUBs indicated that the reduction in risk of PUBs in the etoricoxib group was consistent in the subgroups defined by demographic factors and several potential risk factors for PUBs. The high risk subgroups assessed were history of clinically important GI adverse experience, baseline corticosteroid use, and age (<65 versus ≥65). Although aspirin use is a known GI risk factor, there were too few aspirin users to permit an accurate assessment in this subgroup (Figure 6).

Figure 6

Relative Risk (95% CIs)
Confirmed PUBs: Subgroup Analyses
Active Comparator-Controlled Data Set



Pooled Analysis of GI Tolerability

A pooled analysis of GI tolerability was prespecified and included data from the etoricoxib chronic exposure studies with the exception of data from the 2 surveillance endoscopy studies because these 2 studies were designed differently from the others in excluding any use of gastroprotective agents (GPAs). The GI tolerability endpoints for the pooled analysis fell into 2 different categories, new use of concomitant GPAs and discontinuations due to digestive adverse experiences. The rates of new GPA use in the Active-Comparator-Controlled data set were 8.6 and 12.8 per 100 person-years in the etoricoxib and nonselective NSAID groups, respectively. The etoricoxib-to-nonselective-NSAIDs relative risk (95% CI) of 0.73 (0.61, 0.87; $p<0.001$) was significantly different from 1.0, indicating patients taking etoricoxib were less likely to begin new use of a GPA than patients taking nonselective NSAIDs. These analyses also indicated that etoricoxib patients were less likely to discontinue due to digestive adverse experiences than patients on nonselective NSAIDs. Discontinuation rates due to these adverse experiences were 1.5 and 2.8 per 100 person-years in the etoricoxib and nonselective NSAID groups, respectively. The etoricoxib-to-nonselective-NSAIDs relative risk (95% CI) was 0.57 (0.39, 0.84), which was significantly different from 1.0 ($p=0.004$).

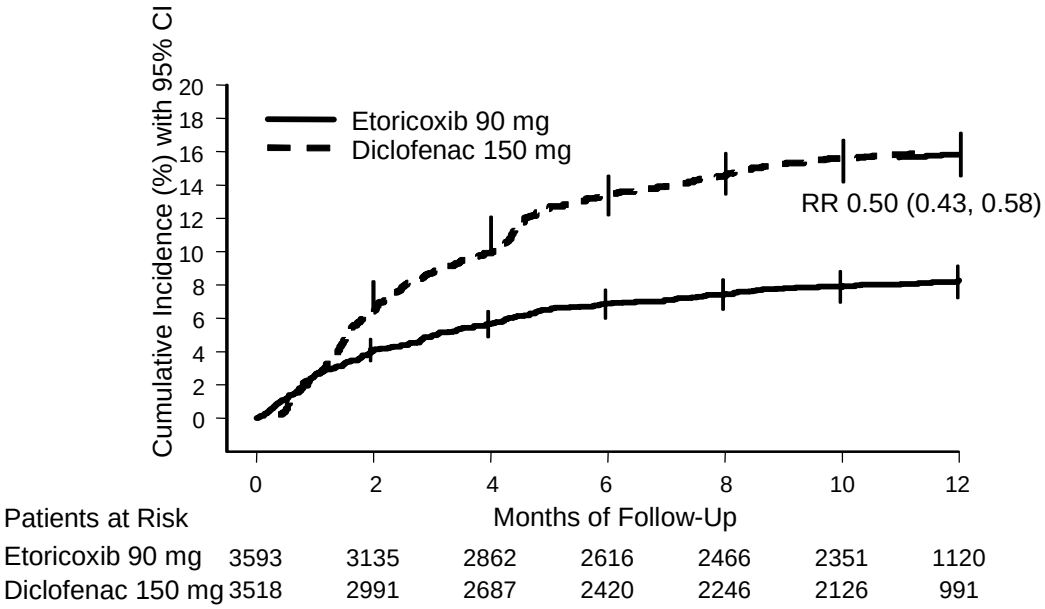
4.4.3 GI Tolerability in the EDGE Study

The EDGE study had as its primary endpoint an assessment of GI tolerability. In this study, GI tolerability was defined as patients discontinuing the study for any clinical or laboratory GI adverse experience. The predefined set of GI adverse experiences included all terms in the Medical Dictionary for Regulatory Affairs (MedDRA) in the GI System Organ Class (with the exception of a small number of terms related to specific oral and dental disorders not deemed clinically relevant) and prespecified adverse experience terms related to liver function abnormalities (i.e., all terms related to hepatic disorder, hepatic failure, hepatic function abnormality, hepatitis, jaundice, alanine amino transferase increased, aspartate aminotransferase increased or bilirubin increased). The primary assessment compared the cumulative incidence of patients discontinuing for a clinical or laboratory GI adverse experience between treatment groups.

The results showed a relative risk (95% CI) of 0.50 (0.43, 0.58) in rates of patient discontinuations for combined clinical and laboratory GI adverse experiences for etoricoxib versus diclofenac, as displayed in a Kaplan-Meier (KM) plot in Figure 7. In KM plots, the number of patients at risk displayed along the x-axis at a given point in time is representative of the number of patients remaining in the study at those time points and therefore, are reflective of the patient number and duration of therapy throughout the study.

Figure 7

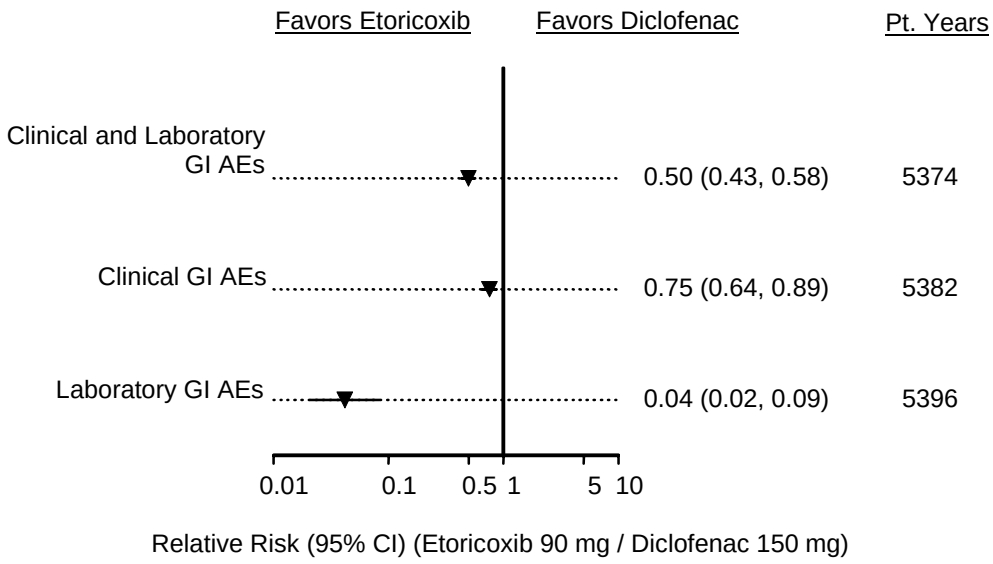
Kaplan-Meier Estimates of Cumulative Incidence of Discontinuations for GI Clinical or Laboratory Adverse Experiences—Primary Endpoint
The EDGE Study



Both components of the primary endpoint (i.e., discontinuation for clinical GI adverse experiences, and for laboratory GI adverse experiences) were associated with a statistically significant reduction, although the magnitude of the risk reduction differed. The relative risk (95% CI) of discontinuations for clinical GI adverse experiences for etoricoxib versus diclofenac was 0.75 (0.64, 0.89) and for laboratory GI adverse experiences was 0.04 (0.02, 0.09) (Figure 8).

Figure 8

Relative Risk (95% CIs)
Primary Endpoint and by Clinical and Laboratory GI Adverse Experiences:
The EDGE Study



PUBs in the EDGE Study

Unlike the studies included in the etoricoxib pooled analysis of PUBs, the EDGE study allowed the unrestricted use of aspirin as well as GPAs which was expected to confound a formal assessment of PUBs in this study. Approximately 18% of the patients started GPAs during the study, defined as beginning GPA therapy after randomization and taking concomitant GPAs for 30 consecutive days or for at least 20% of the total days while taking study therapy. In addition, approximately 31% of the patients also took any dose of aspirin during the study. The protocol prespecified that PUB data from EDGE would be adjudicated and tabulated for completeness, but not formally analyzed, largely based on anticipated use of GPAs and aspirin.

Table 1 shows the analysis of confirmed PUBs for etoricoxib 90 mg versus diclofenac 150 mg daily in the EDGE study. The rates for confirmed PUBs were the same for each treatment group, 1.11 events per 100 patient-years, not unexpected given the use of GPA and aspirin as described.

Table 1

Rates Per 100 Patient Years (95% CI)
Summary of Confirmed PUB
The EDGE Study

	Etoricoxib 90 mg (N=3593)			Diclofenac 150 mg (N=3518)		
	n (%)[†]	Rate[‡]	95% CI	n (%)[†]	Rate[‡]	95% CI
Confirmed PUBs						
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)

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.
[†] Crude incidence rate (%) = (n/N)x 100.
[‡] Rate = Events per 100 patient-years = (n/PYR)x 100.

A subgroup analysis according to aspirin use (defined as postrandomization aspirin use for at least 50% of days on study therapy) was carried out on PUB data from the EDGE study. Non-aspirin users, defined as <50% postrandomization aspirin use, were associated with lower absolute rates of events (0.61 and 0.79 events per 100 patient-years in the etoricoxib and diclofenac groups, respectively), with a numeric difference favoring etoricoxib. Consistent with the primary analysis results, aspirin users were associated with similar rates of events between treatment groups (2.27 and 2.00 events per 100 patient-years in the etoricoxib and diclofenac groups, respectively). A comparison of event rates in aspirin users versus non-users indicates that aspirin use increased the rate of confirmed PUBs by approximately 2- to 4-fold regardless of treatment group (for etoricoxib, the increase was from 0.61 to 2.27 events per 100 patient-years; and for diclofenac from 0.79 to 2.00 events per 100 patient-years). Caution should be used when interpreting subgroup results because total patient exposure and the number of events are limited (Table 2).

Table 2

Rates Per 100-Patient Years (95% CI)
Summary of Confirmed PUB Results by Aspirin Use
The EDGE Study

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 poststudy 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.

4.5 GI Safety and Tolerability Conclusions

- Etoricoxib has a substantially improved GI safety profile compared with nonselective NSAIDs. In 2 large endoscopy studies, etoricoxib 120 mg was associated with an incidence of endoscopic ulcers significantly lower than ibuprofen and naproxen, but greater than placebo. Analysis of all upper GI clinical events demonstrates that etoricoxib use is associated with a consistently lower incidence of upper GI clinical events than nonselective NSAIDs, with the results driven by comparisons to naproxen.
- The GI tolerability profile of etoricoxib is superior to that of nonselective NSAIDs, as evidenced by significantly lower new use of gastroprotective agents and significantly fewer discontinuations due to digestive adverse experiences with etoricoxib than with nonselective NSAIDs. Superior GI tolerability was also established versus diclofenac in the EDGE study.
- Concomitant low-dose aspirin use results in an increased rate of GI ulceration compared to use of etoricoxib alone.
- Overall GI safety and tolerability findings support development of etoricoxib as an alternative therapy with superior GI safety compared to non-selective NSAIDs.

5. Renovascular Safety

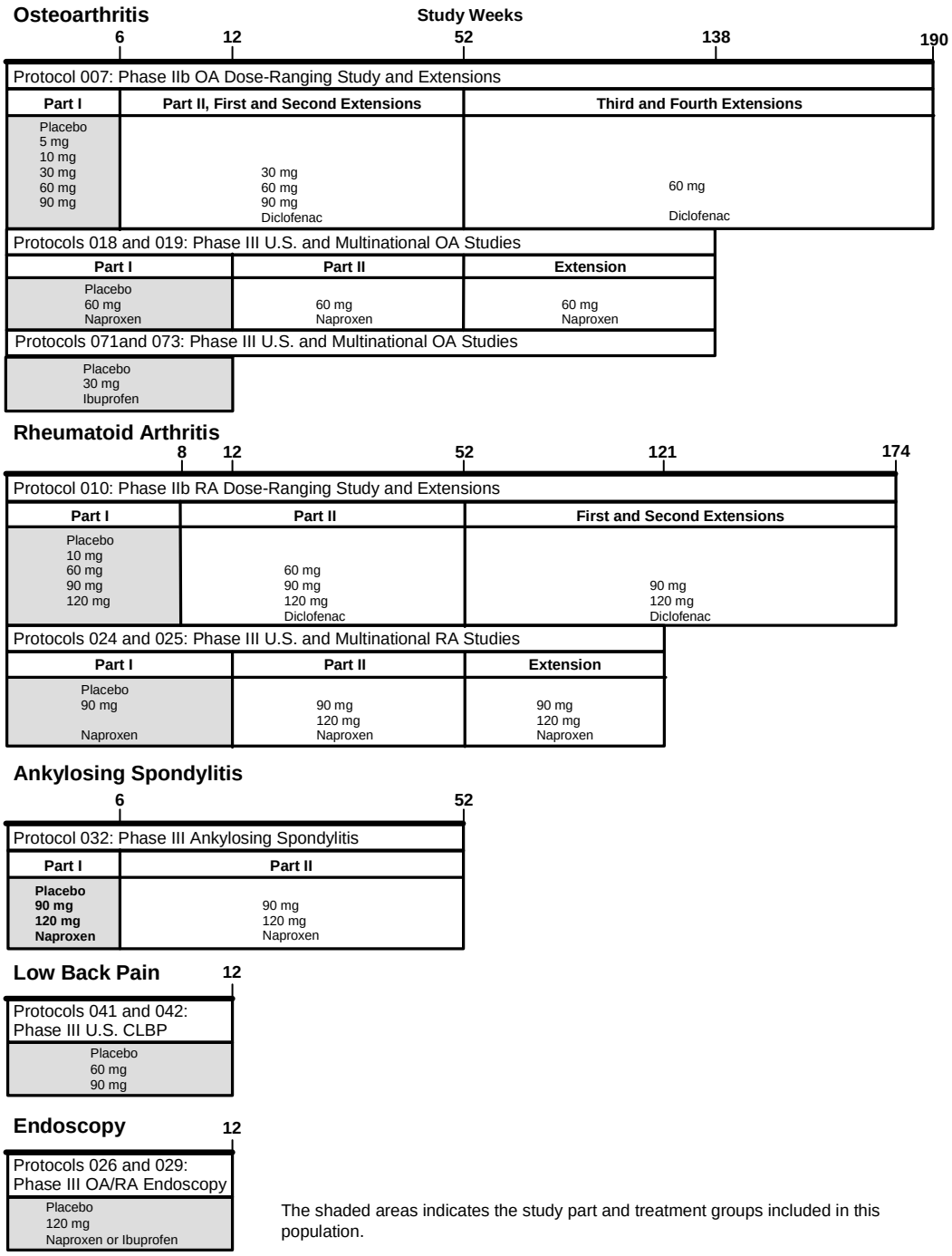
5.1 Background

Renovascular effects (edema, congestive heart failure [CHF], and hypertension) are known dose-related effects of COX inhibition and have been observed with all nonselective NSAIDs [1; 2] and COX-2 inhibitors [3; 4; 5]. To evaluate the clinical impact of these effects, the following analyses of the etoricoxib clinical trials data were prespecified: the incidence of hypertension- and edema-related adverse experiences, the incidence of patients who discontinued from a study due to hypertension- and edema-related adverse experiences, and the incidence of patients with CHF. Adverse experiences were reported by investigators based on their clinical judgment.

As described in Section 1.1, two populations were chosen for presentation of renovascular safety: the Placebo-Controlled Population (Figure 9) and the 1-Year Continuous Exposure, Active-Comparator-Controlled Population (referred to as the 1-Year Active Comparator-Controlled Population) (Figure 10). In the Placebo-Controlled Population, the mean age was approximately 57 years and patients were predominantly white and female. The most frequent secondary medical conditions at baseline included hypertension and hypercholesterolemia (Table 3). In the Placebo-Controlled Population which consists of OA, RA, AS, and CLBP studies, the treatment groups were not balanced in terms of baseline demographics and medical conditions. There were higher proportions of patients with a medical history of hypertension and hypercholesterolemia in the etoricoxib 30- and 60-mg and the NSAID comparator groups compared with those in the placebo and etoricoxib 90- or 120-mg groups. These differences are attributed to the uneven treatment-group distribution across the OA, RA, and CLBP studies. For example, the higher incidence of a medical history of hypertension in the etoricoxib 30-mg, 60-mg, naproxen, and ibuprofen groups was likely reflective of: (1) OA patients comprising the entire etoricoxib 30-mg and ibuprofen groups, two-thirds of the etoricoxib 60-mg group, and approximately half of the naproxen group, and (2) the higher overall incidence of hypertension in OA (42.9%) patients versus RA (25.5%) and CLBP (25.3%) patients. The proportion of patients with a medical history of hypercholesterolemia was higher among OA (17.7%) patients than RA (6.3%) and CLBP (10.4%) patients. In general, there were no other clinically important differences among treatment groups. However, when considering studies within the Placebo-Controlled Population by disease type (e.g., the 5 OA studies), the baseline characteristics were generally similar among treatment groups as expected. Baseline characteristics for the 1-Year Active-Comparator-Controlled Population were generally similar to those described for the Placebo-Controlled Population.

Figure 9

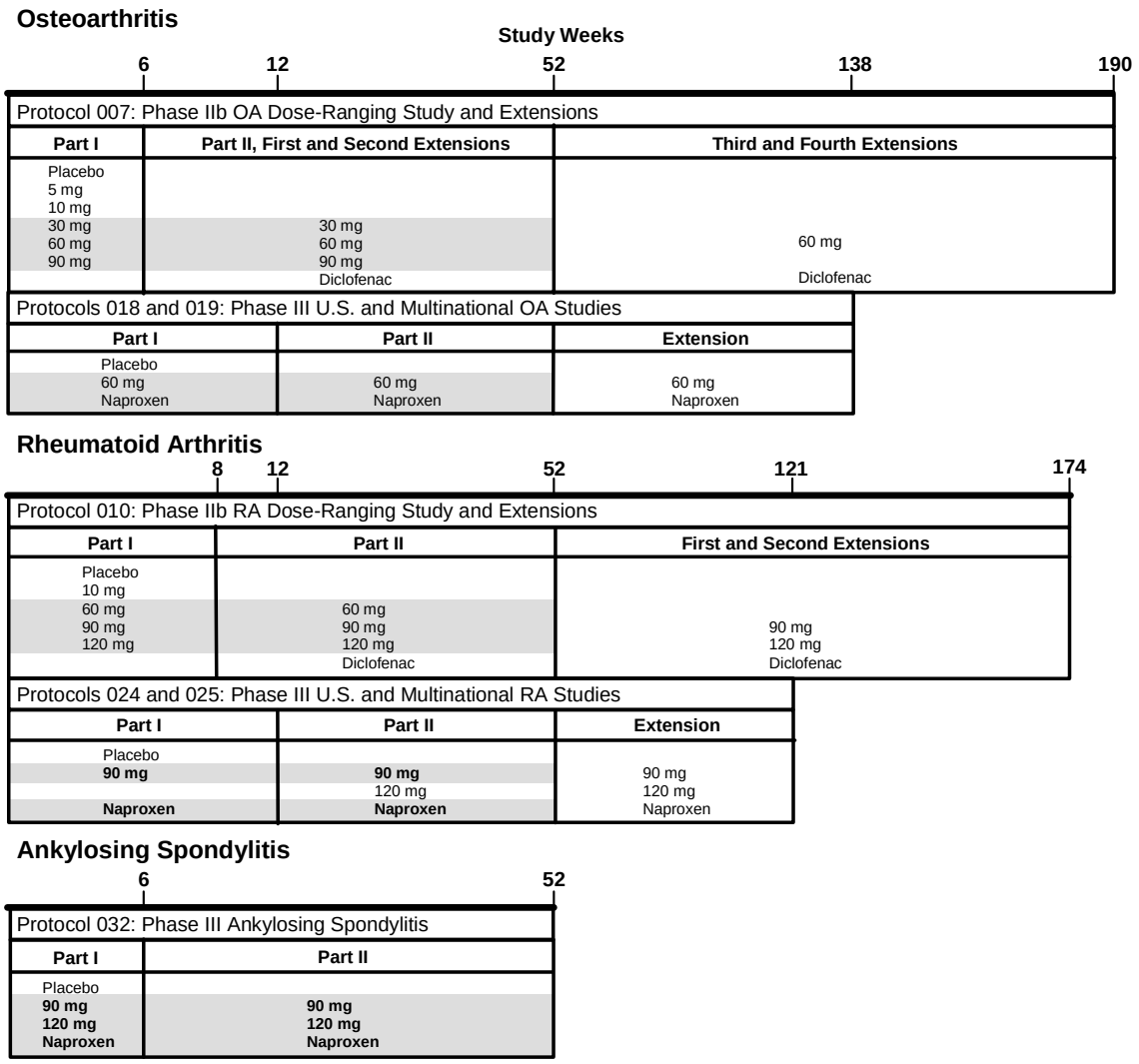
Summary of the Study Portions and Specific Treatment Group Included in the Placebo-Controlled Population



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

Figure 10

Summary of the Study Portions and Specific Treatment Group Included in the 1-Year Continuous Exposure, Active-Comparator-Controlled Population



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

Table 3

Number (%) of Patients With Baseline Hypertension and Hypercholesterolemia
Placebo-Controlled Population and by Disease Type (OA, RA)

	Placebo		Etoricoxib 30 mg		Etoricoxib 60 mg		Etoricoxib 90 mg		Etoricoxib 120 mg		Naproxen 1000 mg		Ibuprofen 2400 mg	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Placebo-Controlled Population	(N=1982)		(N=540)		(N=896)		(N=1238)		(N=684)		(N=1133)		(N=649)	
Hypertension	626	(31.6)	232	(43.0)	317	(35.4)	333	(26.9)	191	(27.9)	382	(33.7)	279	(43.0)
Hypercholesterolemia	188	(9.5)	105	(19.4)	143	(16.0)	109	(8.8)	62	(9.1)	137	(12.1)	101	(15.6)
OA only	(N=680)		(N=540)		(N=558)		(N=112)		(N=288)		(N=494)		(N=649)	
Hypertension	291	(42.8)	232	(43.0)	236	(42.3)	48	(42.9)	112	(38.9)	227	(46.0)	279	(43.0)
Hypercholesterolemia	98	(14.4)	105	(19.4)	112	(20.1)	21	(18.8)	43	(14.9)	98	(19.8)	101	(15.6)
RA only	(N=990)		NA		(N=126)		(N=810)		(N=304)		(N=540)		NA	
Hypertension	271	(27.4)			29	(23.0)	206	(25.4)	67	(22.0)	134	(24.8)		
Hypercholesterolemia	66	(6.7)			3	(2.4)	60	(7.4)	13	(4.3)	32	(5.9)		

Although the Placebo-Controlled Population consists of patients with different study indications, the majority of the patients come from either OA or RA studies. As described above, these two subpopulations are different in terms of demographics (e.g., age, prevalence of concomitant medical conditions) and baseline risk factors that could influence the observed incidence of renovascular effects, particularly hypertension. However, within each subpopulation (i.e., OA separate from RA) baseline demographics and risk factors are similar. For this reason, it is most informative to further analyze the data by disease (specifically OA and RA) in order to maximize the precision with which effects could be observed. In this document, data from the AS and CLBP populations are not described in detail, as they were consistent with data from the larger OA and RA populations.

5.2 Results

5.2.1 Edema- and CHF-Related Adverse Experiences

5.2.1.1 The Placebo-Controlled Population

Edema-related adverse experiences and discontinuations due to these adverse experiences in the Placebo-Controlled Population were prespecified for statistical analyses. Edema-related adverse experiences reported in this population were predefined to include the following adverse experience terms: edema, peripheral edema, lower extremity edema, and fluid retention.

The incidences of edema-related adverse experiences in the Placebo-Controlled Population were 1.8% for placebo; 3.1, 3.8, 2.7, and 2.5% for etoricoxib 30, 60, 90, and 120 mg, respectively; and 2.8, and 5.1% for naproxen, and ibuprofen, respectively. The incidence on etoricoxib 60 mg and ibuprofen were significantly higher than placebo ($p \leq 0.05$). These results do not represent a clear dose response, with an overall incidence on etoricoxib that was generally similar to comparator NSAIDs.

Overall discontinuations due to edema-related adverse experiences were low (<1%) across all treatment groups with no significant differences between any dose of etoricoxib and placebo. The percentage of patients who discontinued due to an edema-related adverse experience was 0.2% for placebo; 0.2, 0.3, 0.2, and 0.1% for etoricoxib 30, 60, 90, and 120 mg, respectively; and 0.1, and 0.8 % for naproxen, and ibuprofen, respectively.

Review of edema-related adverse experiences by subpopulation of disease type (OA, RA, and CLBP) showed results that were generally reflective of the Placebo-Controlled Population (i.e., dose-related increases were not clearly observed, with low incidence of discontinuations).

The most common edema-related adverse experience was lower extremity edema. The incidence of lower extremity edema and discontinuations due to this adverse experience are presented for the Placebo-Controlled Population, as well as for subpopulations by disease type (OA and RA) in Figure 11 and Figure 12, respectively. Overall, the incidence of edema-related adverse experiences on etoricoxib was low and generally similar to comparator NSAIDs.

Figure 11

Incidence of Lower Extremity Edema Adverse Experiences and Discontinuations
Placebo-Controlled Population
All Patients

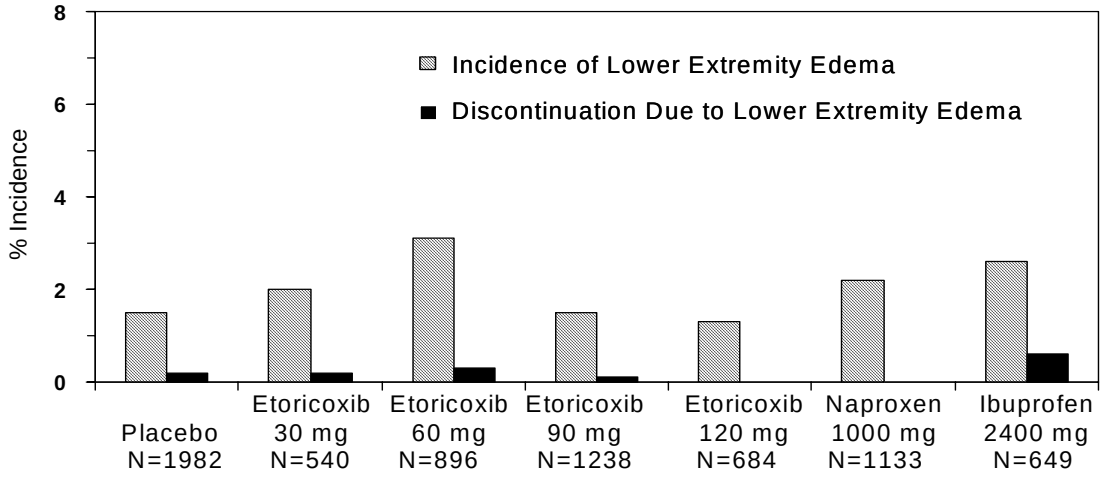
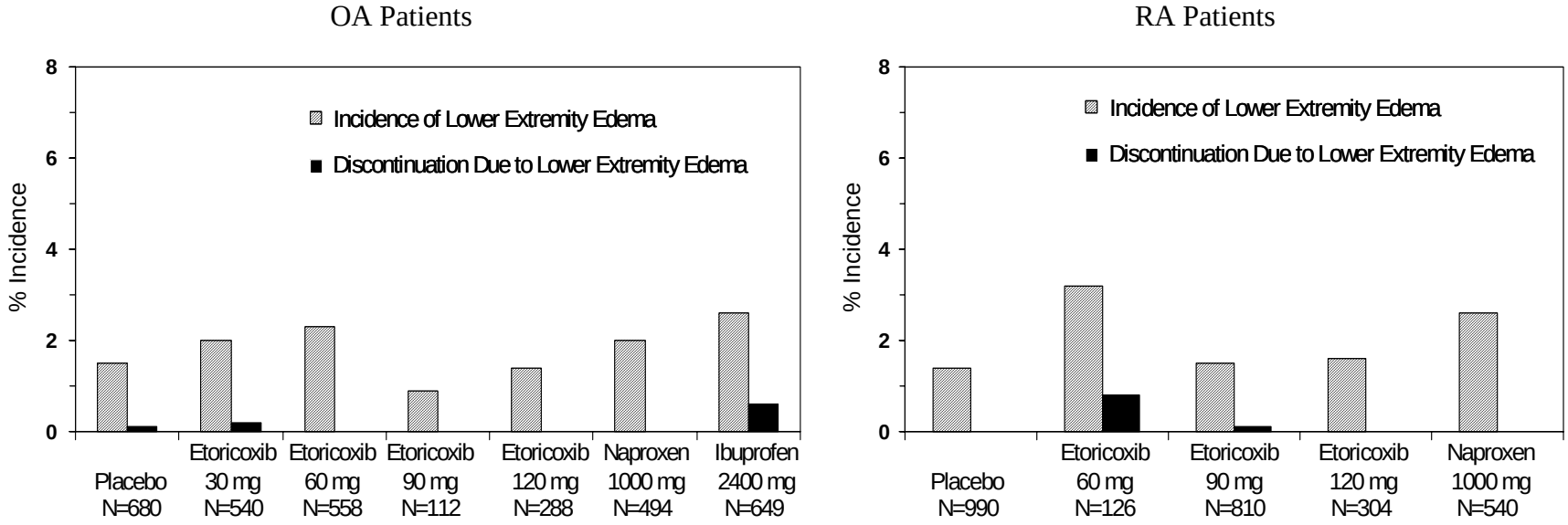


Figure 12

Incidence of Lower Extremity Edema Adverse Experiences and Discontinuations
Placebo-Controlled Population
OA and RA Patients



Adverse Experiences of Congestive Heart Failure

Although rare, CHF is one of the more clinically significant manifestations of the fluid retention that can be caused or exacerbated by nonselective NSAIDs and COX-2 inhibitors. Therefore, CHF were one of the clinical adverse experience categories prespecified for statistical analysis. The overall incidences of CHF were low in all treatment groups (0.0% for placebo; 0.2, 0.3, 0.4, and 0.3% for etoricoxib 30, 60, 90, and 120 mg, respectively; and 0.1, and 0.2 % for naproxen, and ibuprofen, respectively). No dose-related trend was observed across the etoricoxib dose range, although the rate for etoricoxib 90 mg (with 5 patients) was significantly greater than placebo ($p \leq 0.05$). Due to the overall low incidence of CHF, a meaningful analysis of CHF adverse experiences by disease type (i.e., OA, RA) was not possible.

Mean Changes in Body Weight

Examination of body weight, which was measured at scheduled study visits, provides additional context for the interpretation of the mechanism-based, renovascular adverse experiences of edema and CHF. Mean changes from baseline on treatment were small (<1 kg) and not clinically meaningful. Mean changes seen in the etoricoxib groups were generally similar to those observed in the comparator NSAID (naproxen and ibuprofen) groups, with no clear evidence of a dose response. Mean values for body weight for patients on etoricoxib, naproxen, and ibuprofen were generally similar to the values measured at screening (i.e., prior to withdrawal of prestudy NSAIDs).

5.2.1.2 The 1-Year Active-Comparator-Controlled Population

Edema-related adverse experiences and discontinuations due to these adverse experiences were also examined in the 1-Year Active-Comparator-Controlled Population. In this population, data are reported for the etoricoxib 30-mg group (consisting entirely of OA patients) for completeness; however, the interpretation of these data is limited due to the small size (N=55) of the 30-mg treatment group. The incidence of edema-related adverse experiences was generally similar for the etoricoxib 30-mg (3.6%), 60-mg (5.6%), and 90-mg (4.3%), and naproxen groups (5.7%) with a slightly lower incidence for etoricoxib 120 mg (2.4%). In all treatment groups, the incidence of discontinuation due to edema-related adverse experiences was low: 1.8% (1 patient), 0.5% (3 patients), 0.4% (3 patients), 0.0%, and 0.2% (2 patients) discontinued in the etoricoxib 30-mg, 60-mg, 90-mg, 120-mg, and naproxen groups, respectively.

The incidences of edema-related adverse experiences in the subpopulation of OA patients were generally similar between etoricoxib 60 mg (5.3%) and naproxen (6.4%). Comparisons among the etoricoxib doses are limited due to the small number of patients in the 30- and 90-mg etoricoxib groups (N=55 and 112, respectively). In RA patients, a lower incidence was observed on etoricoxib 90 (3.9%) and 120 mg (2.5%) compared with etoricoxib 60 mg (8.3%) or naproxen (6.0%), with the relatively small sample size of the etoricoxib 60-mg group (N=60) limiting further interpretation. In both the OA and RA populations, no more than 2 patients in any individual treatment group discontinued due to edema-related adverse experiences.

As observed in the Placebo-Controlled Population, the most common edema-related adverse experience was lower extremity edema. The incidence of lower extremity edema and discontinuations due to this event are presented for the 1-Year Active-Comparator-Controlled Population, as well as subpopulations by disease type (OA and RA) in Figure 13 and Figure 14, respectively. Consistent with the results of the Placebo-Controlled Population, the incidence of edema-related adverse experiences on etoricoxib over a 1-year treatment period was low and generally similar to comparator the NSAID, naproxen.

Figure 13

Incidence of Lower Extremity Edema Adverse Experiences and Discontinuations
1-Year Active-Comparator-Controlled Population
All Patients

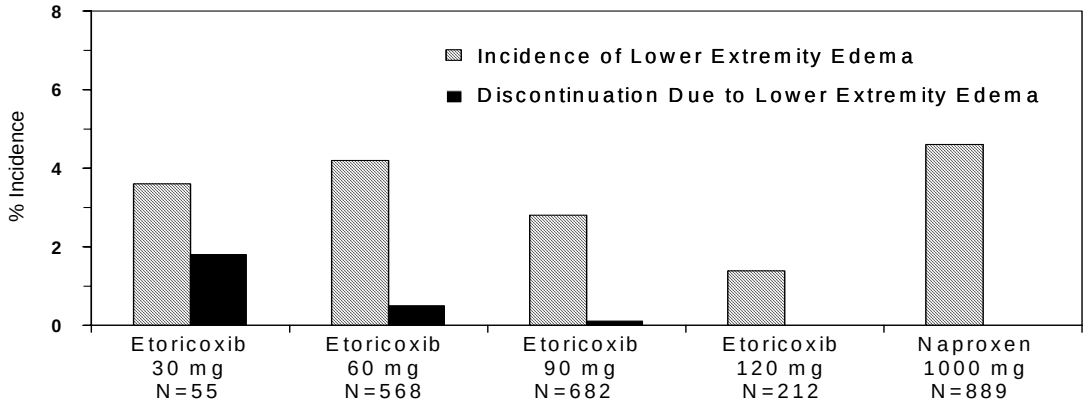
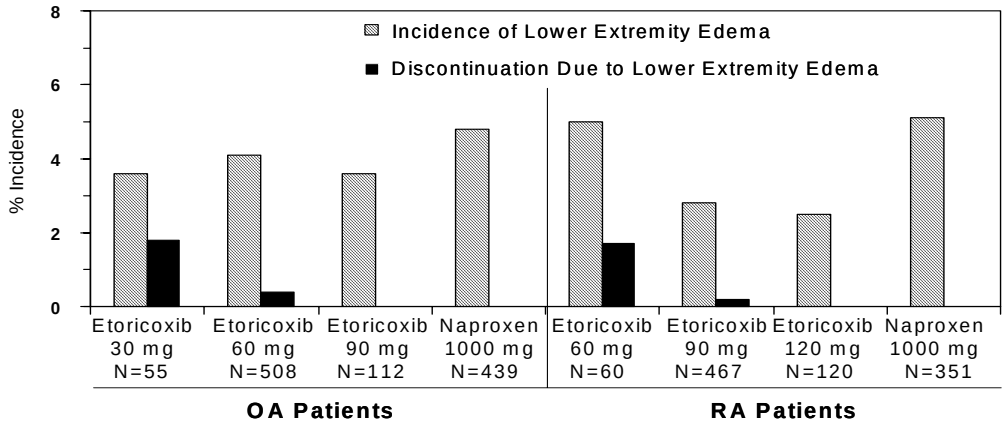


Figure 14

Incidence of Lower Extremity Edema Adverse Experiences and Discontinuations
1-Year Active-Comparator-Controlled Population
OA and RA Patients



Adverse Experiences of Congestive Heart Failure

Less than 1% of the patients in the 1-Year Active-Comparator-Controlled Population had a CHF-related adverse experience. Overall incidences were generally similar among all treatment groups: 0.0%, 0.4% (2 patients), 0.4% (3 patients), 0.9% (2 patients), and 0.2% (2 patients) on etoricoxib 30 mg, 60 mg, 90 mg, 120 mg, and naproxen, respectively.

Mean Changes in Body Weight

Patients in the etoricoxib 60-mg and 90-mg groups had similar small (<1 kg) changes from baseline in body weight over the 1-year continuous exposure period. In the naproxen group, the mean changes from baseline were slightly higher (the maximum value was 1.1 kg on naproxen compared with the maximum value of approximately 0.60 kg on etoricoxib 60 or 90 mg).

Edema- and CHF-Related Adverse Experiences in the EDGE Study

In the EDGE study, the incidence of edema-related adverse experiences was numerically higher on etoricoxib 90 mg (7.5%) compared to diclofenac 150 mg (5.9%), and discontinuations resulting from edema-related adverse experiences were low and similar between etoricoxib (0.9%) and diclofenac (0.7%). The most common specific edema-related adverse experience resulting in discontinuation was peripheral edema, which occurred at a similar frequency in both treatment groups. None of the adverse experiences were considered serious. The incidence of CHF-related adverse experiences was low in both treatment groups (0.4% and 0.2% in the etoricoxib and diclofenac treatment groups, respectively).

5.2.2 Hypertension-Related Adverse Experiences

5.2.2.1 The Placebo-Controlled Population

The incidence of hypertension-related adverse experiences and discontinuations due to these adverse experiences were prespecified for statistical analyses in the Placebo-Controlled Population. Hypertension-related adverse experiences reported in this population were predefined to include the following adverse experience terms: blood pressure increased, borderline hypertension, diastolic hypertension, hypertension, hypertensive crisis, labile hypertension, systolic hypertension, and uncontrolled hypertension.

In the Placebo-Controlled Population, a shallow dose response was observed in the incidence of hypertension-related adverse experiences on etoricoxib, with an overall incidence on etoricoxib that was generally similar to naproxen and slightly lower than ibuprofen: incidences were 2.4% for placebo; 3.9, 3.9, 4.1, and 4.7% for etoricoxib 30, 60, 90, and 120 mg, respectively; and 3.6, and 6.6% for naproxen, and ibuprofen, respectively. Rates on etoricoxib 90 mg and ibuprofen were significantly higher than placebo ($p \leq 0.001$ for the difference between etoricoxib 90 mg and placebo, and $p \leq 0.05$ for the difference between ibuprofen and placebo).

Discontinuations due to hypertension-related adverse experiences were uncommon in all treatment groups. The percentage of patients who discontinued due to a hypertension-related adverse experience was 0.1% for placebo; 0.7, 0.2, 0.2, and 0.4% for etoricoxib 30, 60, 90, and 120 mg, respectively; and 0.3 and 0.8 % for naproxen, and ibuprofen, respectively. No significant differences in the incidence of discontinuation were seen between etoricoxib and placebo.

Review of hypertension-related adverse experiences by disease type (OA, RA, and CLBP) indicates evidence of a dose response, most apparent in the OA subpopulation, with incidences of 3.9, 4.8, 3.6, and 6.6% on etoricoxib 30 mg, 60 mg, 90 mg, and 120 mg, respectively; compared with 3.8% on placebo, 4.0% on naproxen, and 6.6% on ibuprofen. At the highest etoricoxib dose of 120 mg (twice the dose recommended for chronic use in OA), the incidence was similar to ibuprofen.

The most frequently occurring hypertension-related adverse experience was the specific adverse experience of hypertension. The incidence of hypertension adverse experiences and discontinuations due to this adverse experience are presented for the Placebo-Controlled Population, and for subpopulations by disease type (OA and RA) in Figure 15 and Figure 16, respectively.

Analyses using a Kaplan-Meier approach were also performed to further evaluate hypertension-related adverse experiences on etoricoxib over the 12 week duration of the Placebo-Controlled Population (Figure 17). All doses of etoricoxib were combined and compared to placebo for this evaluation. In OA, this included doses of 30, 60, and 90 mg; in RA, doses of 60, 90, and 120 mg were combined for comparisons. The KM plot shows that the cumulative incidences of hypertension-related adverse experiences were generally constant over the 3-month period.

Figure 15

Incidence of Hypertension Adverse Experiences and Discontinuations
Placebo-Controlled Population
All Patients

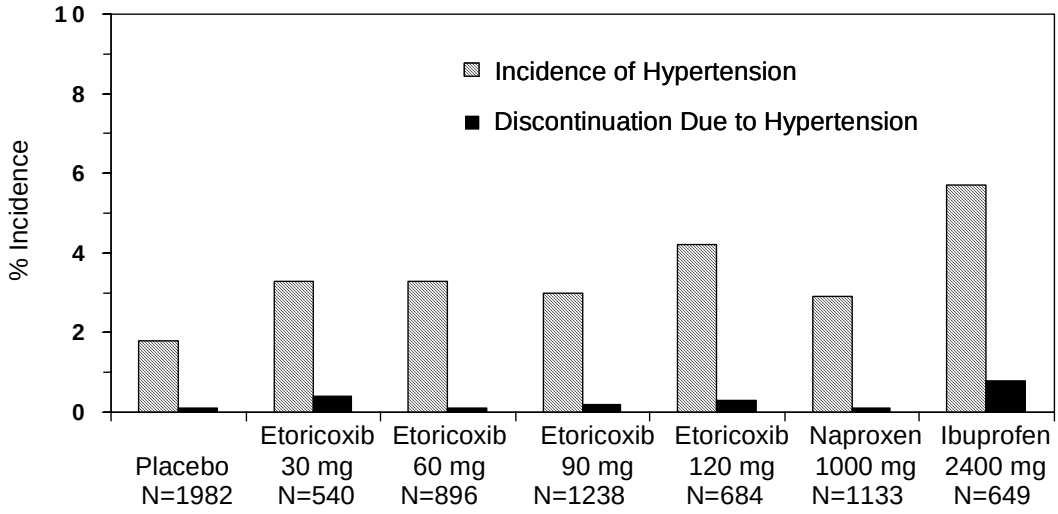


Figure 16

Incidence of Hypertension Adverse Experiences and Discontinuations
Placebo-Controlled Population
OA and RA Patients

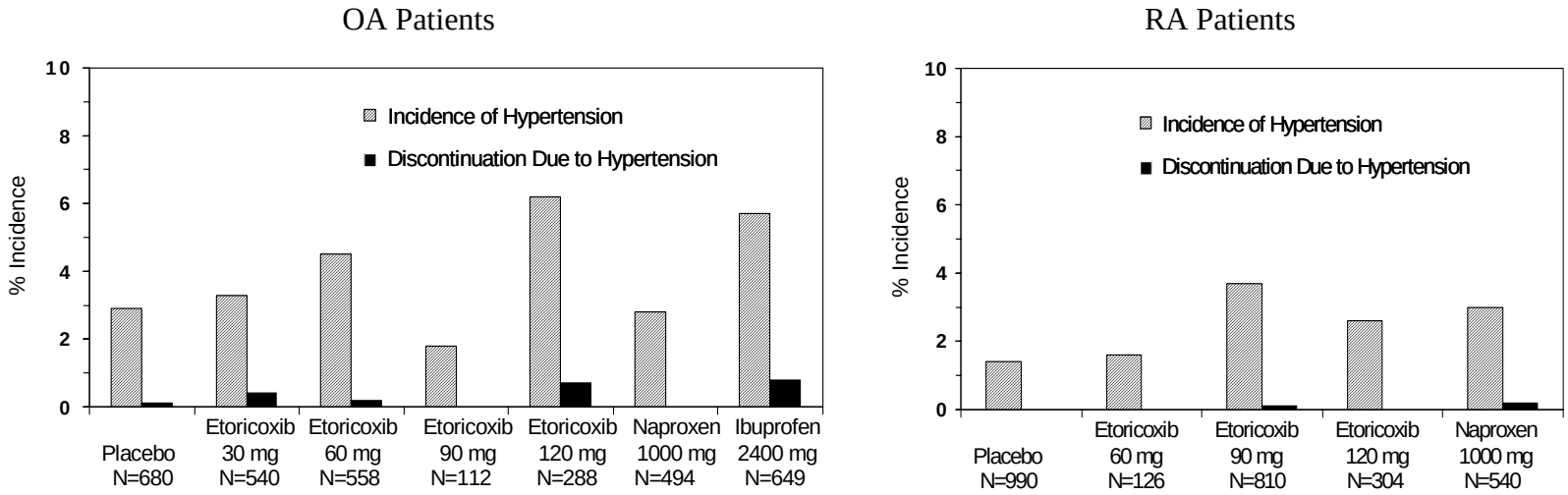
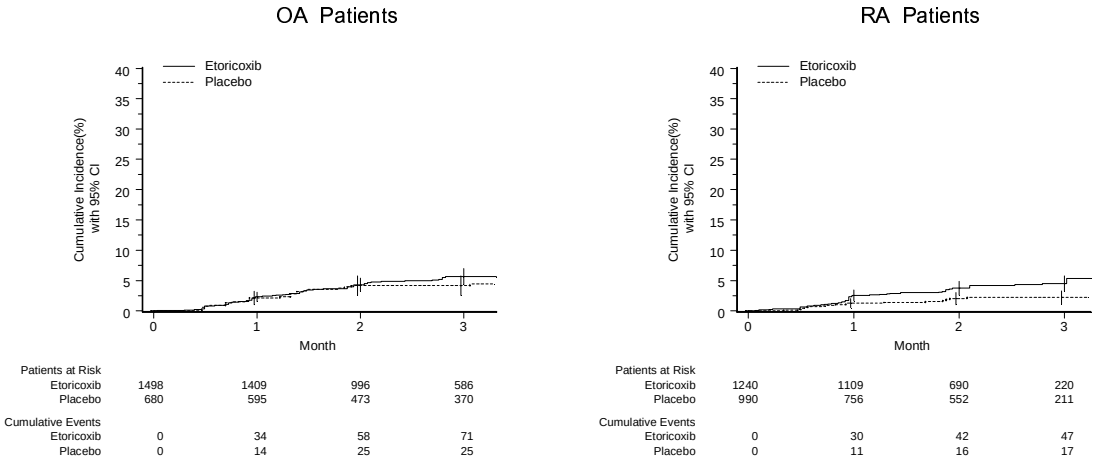


Figure 17

Kaplan-Meier Estimates of Cumulative Incidence of
Hypertension-Related Adverse Experiences
Placebo-Controlled Population
OA and RA Patients



Patients at Risk				
Etoricoxib	1498	1409	996	586
Placebo	680	595	473	370
Cumulative Events				
Etoricoxib	0	34	58	71
Placebo	0	14	25	25

Patients at Risk				
Etoricoxib	1240	1109	690	220
Placebo	990	756	552	211
Cumulative Events				
Etoricoxib	0	30	42	47
Placebo	0	11	16	17

Mean Changes in Systolic and Diastolic Blood Pressure

Blood pressure measurements were obtained at all scheduled study visits. In the Placebo-Controlled Population, results for mean changes in systolic blood pressure were generally similar across treatment groups. Baseline measurements of blood pressure were performed at a single randomization visit after NSAID washout. In some studies, blood pressure values were an average of 2 or 3 readings while in other studies they represented a single reading. Mean changes from baseline in systolic blood pressure ranged from 0.9 to 2.1 mm Hg over the 12-week period across all doses of etoricoxib—a range that was slightly higher than naproxen (ranged from -1.3 to 0.6 mm Hg) but similar to ibuprofen (ranged from 1.2 to 3.2 mm Hg). Mean changes from baseline in diastolic blood pressure for the all etoricoxib groups were small (≤1.1 mm Hg) and similar to both naproxen and ibuprofen.

Results for the OA and RA subpopulations were generally similar to those observed for the combined Placebo-Controlled Population. There were small increases in systolic blood pressure in all active-treatment groups, which generally returned to approximately the point they were at screening (prior to discontinuing prestudy NSAID).

In the naproxen group, mean decreases from baseline (albeit smaller) were also observed at Week 6 and Week 9.

5.2.2.2 The 1-Year Active-Comparator-Controlled Population

The incidence of hypertension-related adverse experiences and discontinuations due to these adverse experiences were also examined in the 1-Year Active-Comparator-Controlled Population. As noted previously, interpretation of etoricoxib 30-mg data (consisting entirely of OA patients) is very limited due to the small sample size (N=55). The overall incidence was generally similar among the treatment groups, with the exception of the etoricoxib 60-mg group (11.1%). The increase on etoricoxib 60 mg did not extend to etoricoxib 90 (9.1%) and 120 mg (7.5%) which were numerically similar to naproxen (7.6%). The incidence of discontinuation due to hypertension-related adverse experiences was low: 0.0% (0 patients), 0.5% (3 patients), 0.1% (1 patient), 0.5% (1 patient), and 0.3% (3 patients) discontinued in the etoricoxib 30-mg, 60-mg, 90-mg, 120-mg, and naproxen groups, respectively.

The incidence of hypertension-related adverse experiences by disease type was generally consistent with the results for the entire 1-Year Population, yet provides some additional information for the interpretation of the results. In the OA subpopulation, although a higher incidence of hypertension-related adverse experiences in the etoricoxib 60-mg group (11.8%) is observed compared to the other treatment groups (including etoricoxib 30 mg [7.3%]), similar rates were observed with 90-mg group (9.8%) and naproxen (8.4%). In RA patients, no clinically meaningful between-group differences were observed in the incidence of hypertension-related adverse experiences among all treatment groups, with the lowest incidence on etoricoxib 60 mg (5.0, 9.2, 8.3, and 7.1% of the patients in the etoricoxib 60-mg, 90-mg, 120-mg, and naproxen groups, respectively). In both the OA and RA populations, discontinuation rates due to hypertension-related adverse experiences were low (<1.0%) in all treatment groups, with no discontinuations for RA patients on any dose of etoricoxib.

As in the Placebo-Controlled Population, the most frequently occurring hypertension-related adverse experience was the specific adverse experience term hypertension. The incidence of hypertension adverse experiences and discontinuations due to this adverse experience are presented for the 1-Year Active-Comparator-Controlled Population, and for subpopulations by disease type (OA and RA) in Figure 18 and Figure 19, respectively. The incidence of hypertension was generally similar to naproxen in the 1-Year Active-Comparator-Controlled Population. A dose-related trend is observed across the etoricoxib doses when evaluating hypertension by disease (OA and RA). The incidence of discontinuations was low across all treatment groups in these studies.

In order to further evaluate the effect of etoricoxib on blood pressure, analyses using a Kaplan-Meier approach were performed to characterize the cumulative incidence of hypertension-related adverse experiences on etoricoxib over an extended period of time (beyond 1 year): approximately 30 to 36 months when compared with nonselective NSAIDs (Figure 20). Etoricoxib doses were combined and are represented by a single

group (doses of 30, 60 and 90 mg for OA; 60, 90 and 120 mg for RA), as are the NSAID comparators. In the RA population, both etoricoxib and comparator NSAID incidence curves can be seen moving in parallel with generally overlapping confidence intervals out to approximately 24 months (2 years). Although there are small differences in the incidence of hypertension-related adverse experiences after this time point, these differences occur at a point in time when the majority of trials (including extensions) have completed, and the number of RA patients at risk is limited (about 10% of the number of patients at risk at baseline). In OA patients, the cumulative incidence rate of hypertension for both etoricoxib and comparator NSAIDs remained generally constant over time.

Figure 18

Incidence of Hypertension Adverse Experiences and Discontinuations
1-Year Active-Comparator-Controlled Population
All Patients

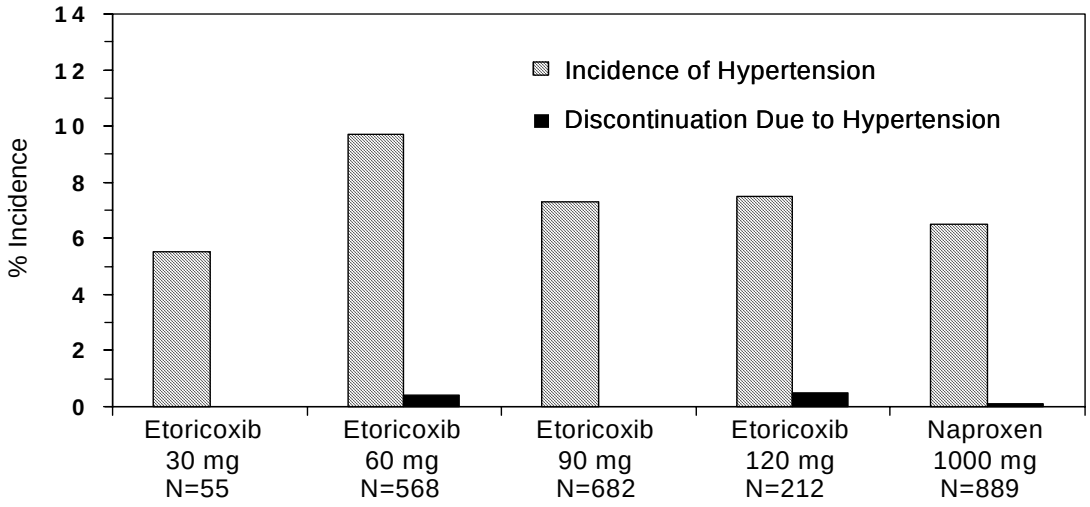


Figure 19

Incidence of Hypertension Adverse Experiences and Discontinuations
1-Year Active-Comparator-Controlled Population
OA and RA Patients

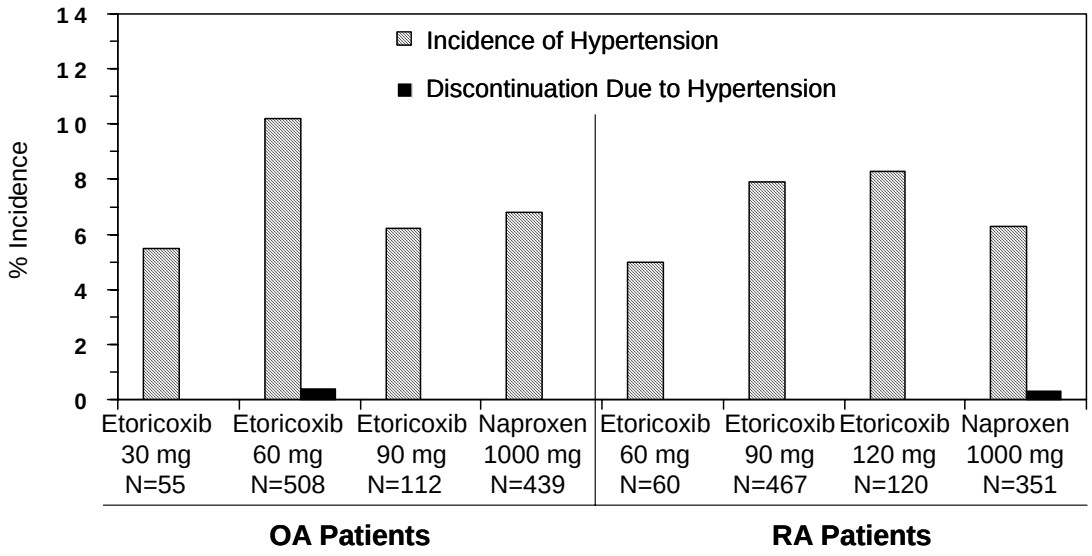
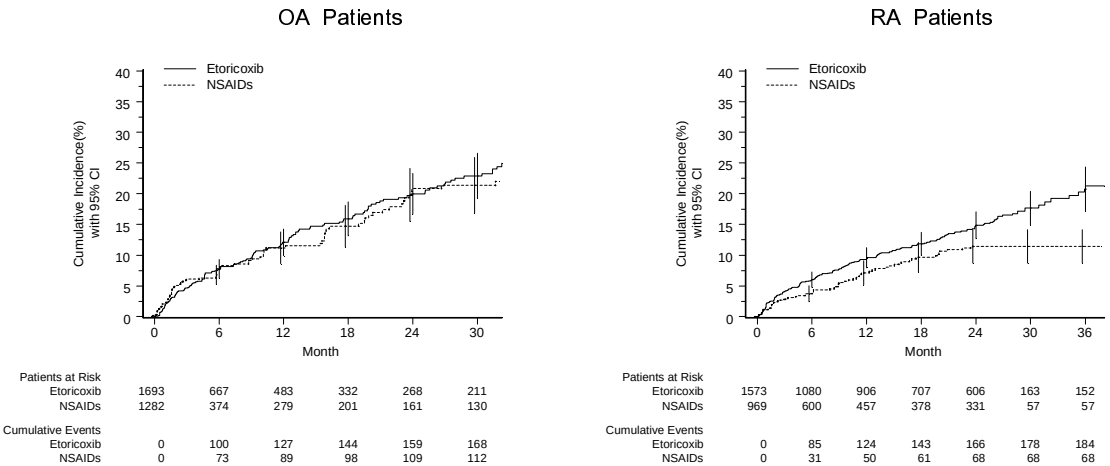


Figure 20

Kaplan-Meier Estimates of Cumulative Incidence of
Hypertension-Related Adverse Experiences
Active-Comparator-Controlled Population (Beyond 1 Year)
OA and RA Patients



Mean Changes in Systolic and Diastolic Blood Pressure

Results for mean changes in systolic blood pressure over 1 year were generally similar to those obtained at 12 weeks in the Placebo-Controlled population. Over the course of 1 year, the mean changes in blood pressure did not vary in a clinically meaningful way from prestudy NSAID levels. Mean changes from baseline in systolic blood pressure ranged from 1.6 mm Hg to 2.8 mm Hg for etoricoxib 60 mg; 1.5 to 3. 2 mm Hg for etoricoxib 90 mg; 0.4 to 2.9 mm Hg for etoricoxib 120 mg; and 0 to 1 mm Hg for naproxen. Mean changes in diastolic blood pressure for etoricoxib were likewise small and not clinically meaningful. Mean changes from baseline in diastolic blood pressure ranged from 0.4 to 1.1 mm Hg for etoricoxib 60 mg, 0 to 0.6 mm Hg for the etoricoxib 90 mg; -0.4 to 1.1 mm Hg for etoricoxib 120 mg; and -0.5 to 0.1 mm Hg for naproxen.

Consistent with the combined 1-Year Population, no increased effects on blood pressure were observed over time for OA or RA patients.

Hypertension-Related Adverse Experiences in the EDGE Study

In the EDGE study, a higher incidence of hypertension-related adverse experiences was observed for etoricoxib 90 mg (11.7%) than for diclofenac 150 mg (5.9%). The percentage of patients discontinuing from the study due to hypertension-related adverse experiences on etoricoxib and diclofenac were 2.3% and 0.7%, respectively ($p<0.001$). The most common specific hypertension-related adverse experience term reported was hypertension.

Given the known dose-related renovascular effects of NSAIDs [1; 2] and COX-2 inhibitors [3; 4; 5], including etoricoxib [41], the effects of etoricoxib on blood pressure observed in EDGE are not unexpected given that the 90 mg was the dose used in this study, a dose 50% higher than is recommended for chronic use in OA and a dose associated with detectable effects on blood pressure as detailed previously. Data from an additional non-IND OA study (Protocol 805) showed similar incidences of hypertension-related adverse experiences for etoricoxib 60 mg (4.3%) and for diclofenac 150 mg (4.6%). Although hypertension-related adverse experiences occurred at a higher rate on etoricoxib 90 mg versus diclofenac in the EDGE study, these rates were generally similar to those observed with 90 mg in the etoricoxib development program, in which the effects were generally similar to NSAIDs evaluated in those studies.

5.3 Renovascular Safety Conclusions

- The incidence of edema- and CHF-related adverse experiences on etoricoxib is low overall and generally similar to that on comparator NSAIDs.
- Etoricoxib, at doses currently developed for chronic use (60 mg, and 90 mg), and extending up to the dose developed for acute pain and acute gouty arthritis (120 mg), manifests effects on blood pressure that are generally similar to NSAIDs. There is evidence for a shallow dose-related trend for etoricoxib in the incidence of hypertension-related adverse experiences, most apparent in analyses of data within individual disease types.

6. Cardiovascular Safety

6.1 Overview and Introduction

This section provides a comprehensive review of the CV safety data from the etoricoxib development program.

6.1.1 Effects of Aspirin, Selective COX-2 Inhibitors, and Nonselective NSAIDs on Thromboxane and Prostacyclin Synthesis

Cyclooxygenase and its prostanoid products have important roles in both inflammation and hemostasis. It is thought that COX-mediated hemostatic effects are primarily mediated by 2 prostanoids, thromboxane A_2 (TXA_2) and prostacyclin (PGI_2).

6.1.1.1 The Effects of Selective COX-2 Inhibitors and of Nonselective NSAIDs on Prostacyclin Synthesis

Merck collaborated with external investigators to investigate the effects of selective COX-2 inhibitors on prostanoid production [3]. Similar research had been performed using celecoxib [42]. These studies demonstrated that selective COX-2 inhibitors reduced the urinary excretion of the prostacyclin metabolite PGI-M. These data demonstrated that COX-2 was important in systemic prostacyclin production. In these experiments, selective COX-2 inhibitors and nonselective NSAIDs appeared to inhibit the excretion of PGI-M to a similar extent (50-70%). Thus, these data were interpreted to suggest that COX-2 is the dominant cyclooxygenase isoform involved in systemic prostacyclin production. With the advent of better measurement techniques, subsequent experiments have shown clinical doses of non-selective NSAIDs such as naproxen inhibit the excretion of the prostacyclin metabolite PGI-M to a somewhat greater extent than clinical doses of selective COX-2 inhibitors, suggesting that both COX isoforms participate in systemic prostacyclin production, although COX-2 is the dominant component. Such data included a placebo-controlled study which evaluated the effects of etoricoxib 90 mg once daily, celecoxib 200 mg twice daily, and naproxen 500 mg twice daily on the urinary excretion of prostanoids; PGI-M, and 11-dehydro TXB_2 (a measure of systemic thromboxane production). Percent change from baseline for PGI-M (pg/mg Creatinine) at Day 15 for placebo, etoricoxib, celecoxib, and naproxen was -6.2, -57.9, -57.2 and -76.2%, respectively (all active treatments vs placebo change from baseline, $p<0.05$). Similar to placebo, etoricoxib and celecoxib had no clinically apparent effect on systemic thromboxane production as assessed by urinary 11-dehydro TXB_2. In contrast, naproxen showed a significant reduction in urinary 11-dehydro TXB_2.

The experiments cited above did not reveal the source of the COX-2-dependent systemic prostacyclin. Endothelial cells express abundant COX-1 but have been shown in vitro to express COX-2 under certain pathologic conditions or under sheer stress [43; 44]. Although prostacyclin is produced in endothelium, it is also produced in other tissues such as lung. Nonetheless, based on the earlier experiments showing that cultured endothelial cells could upregulate COX-2 expression in certain conditions, it was hypothesized that at least some of the COX-2-dependent systemic prostacyclin was

derived from endothelium. It was hypothesized that inhibition of endothelial prostacyclin synthesis by a selective COX-2 inhibitor without the inhibition of platelet thromboxane synthesis as would be obtained with a non-selective inhibitor of both COX-1 and COX-2 could theoretically alter the hemostatic balance achieved by prostacyclin and thromboxane. And it was hypothesized that this imbalance could theoretically be prothrombotic and lead to an increase in the risk of thrombotic cardiovascular events.

Since 1998, we and other researchers have investigated the potential source of the prostacyclin metabolites in urine that are decreased after administration of either non-selective NSAIDs or selective COX-2 inhibitors [3; 42]. Rabbit and dog studies conducted by Merck Frosst laboratories have suggested that arterial prostacyclin production is mediated by COX-1 rather than COX-2 [45; 46]. Others have come to similar conclusions based on studies in rat tissues [47]. Further, in an arm laceration study that measured prostacyclin metabolites at the site of injury, Tuleja and colleagues [48] observed that rofecoxib did not reduce prostacyclin metabolite levels and concluded that in human microvasculature, COX-1, and not COX-2, appears to be the source of prostacyclin [48]. Nevertheless, experiments with cultured human endothelial cells under sheer stress [44; 43] reveals an upregulation of COX-2 expression, so other components of the vasculature may be considered [49; 50]. Thus, to this day, the origin of COX-2 dependent systemic prostacyclin remains to be established.

6.1.1.2 Comparison of the Effects of Selective Cox-2 Inhibitors and Nonselective NSAIDs/Aspirin on COX-1-Related Platelet Metabolism

Clinical Pharmacology Data

As clinical use of NSAIDs increased, the ENT literature discussed an association of NSAID therapy with epistaxis, and inhibition of platelet aggregation with increased bleeding after non-selective NSAID administration was noted in the surgical literature as well [51; 52; 53; 54; 55]. The effects of NSAIDs on platelet aggregation were found to be related to the inhibition of COX-1 mediated TXA_2 synthesis [56] and it was recognized that the effect of an NSAID on platelet aggregation was related to the duration of the drug's effect on TXA_2 synthesis [57].

It is thought that, to serve as a vascular-protective agent, near-complete inhibition of TXA_2 synthesis sustained over time is needed [58]. The effect of chronic therapy with non-aspirin COX-1/COX-2 inhibitors (the nonselective NSAIDs) on the incidence of cardiovascular thrombotic events has not been well characterized. Although nonselective NSAIDs inhibit platelet COX-1 activity, this inhibition is reversible. Thus, the ability of a nonselective NSAID to provide potent and sustained antiplatelet effects that mimic aspirin's antiplatelet properties (and thus potentially to produce aspirin-like vascular-protection) is highly dependent on the unique COX-1/COX-2 potency and pharmacokinetic profiles of each of these compounds. In contrast to the nonselective NSAIDs or aspirin, selective COX-2 inhibitors do not have these platelet inhibitory effects because platelets do not express COX-2 [59].

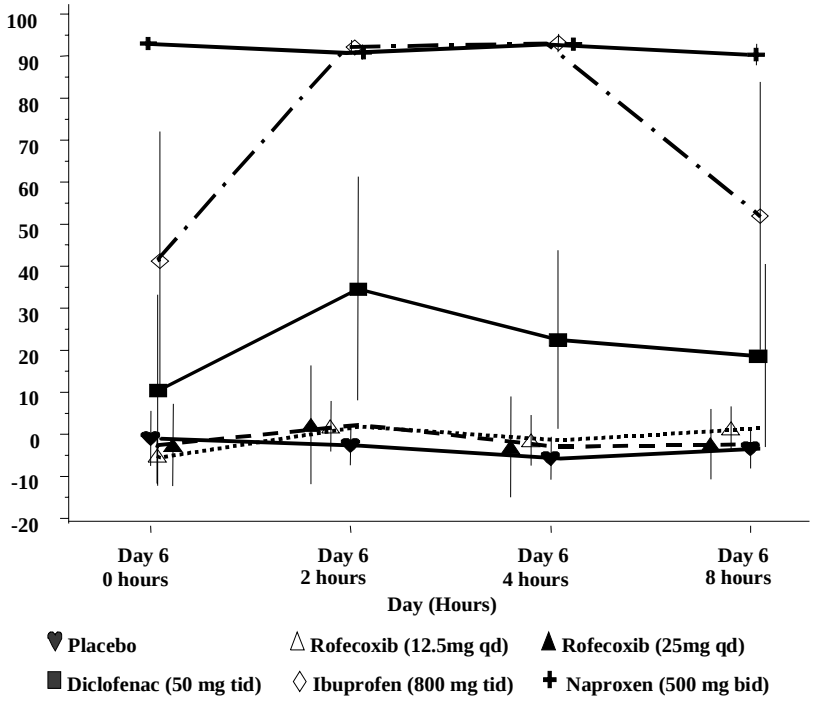
Several studies have demonstrated that the nonselective NSAIDs vary in the magnitude and time course of their effects on platelet function. These studies evaluated the effects of the NSAIDs on thromboxane metabolism and platelet aggregation in normal subjects. TXA_2 synthesis by platelets was monitored by measuring serum TXB_2 generated in clotting whole blood. As blood coagulates, platelets synthesize and release TXA_2. The synthesis of TXA_2 is dependent on COX-1. TXA_2 is converted rapidly and non-enzymatically to TXB_2 which is stable and measurable. In addition to the measurement of these prostanoid metabolites, effects on platelet aggregation and bleeding time were studied.

Studies have been performed comparing the effects of the selective COX-2 inhibitor rofecoxib and several nonselective NSAIDs on thromboxane generation and platelet function [7]. In the first study, patients were randomized to receive 6 days of therapy with either placebo, rofecoxib 12.5 or 25 mg once daily, diclofenac 50 mg 3 times daily, ibuprofen 800 mg 3 times daily, or naproxen 500 mg 2 times daily. The effects of these therapies on COX-1 activity were assessed by measuring the inhibition of TXB_2 generation and arachidonic acid-induced platelet aggregation at steady state. On day 6, measurements were taken prior to (trough) and at several times points after dosing. A second study investigated the effect of low-dose aspirin (81 mg) on TXB_2 and platelet aggregation and assessed the subsequent effect of rofecoxib 50 mg once daily on the aspirin-induced inhibition of TXB_2 and platelet aggregation.

The inhibition of platelet aggregation across the dosing intervals is displayed in Figure 21. In this figure, the effect of each drug is displayed across it's recommended dosing interval. Because the study was performed at steady-state, measurements at 0 hours represent the trough values for the previous dose. These data show a gradient of platelet aggregatory effects when the pharmacodynamics of each drug is taken into account. Rofecoxib had an effect similar to placebo and diclofenac had an intermediate effect. Although ibuprofen showed near maximal inhibition, it was not maintained across the dosing interval. Only naproxen resulted in near maximal inhibition of platelet aggregation that was maintained across its dosing interval. The inhibition observed for naproxen in the first study was similar to that observed for aspirin in the second study. Naproxen also inhibited platelet thromboxane by > 90% across the dosing interval, a level also achieved with aspirin.

Figure 21

Percent Inhibition From Baseline Platelet Aggregation by
Time Point on Day 6 Using Arachidonic Acid as Agonist (Mean ±90% CI)



Also consistent with these data, therapy with placebo, rofecoxib, and diclofenac did not result in a prolongation of bleeding time whereas therapy with naproxen 500 mg twice daily prolonged bleeding time by ~79% [6]. This effect of naproxen on bleeding time is similar to the reported effect of aspirin (50-100% prolongation) [60].

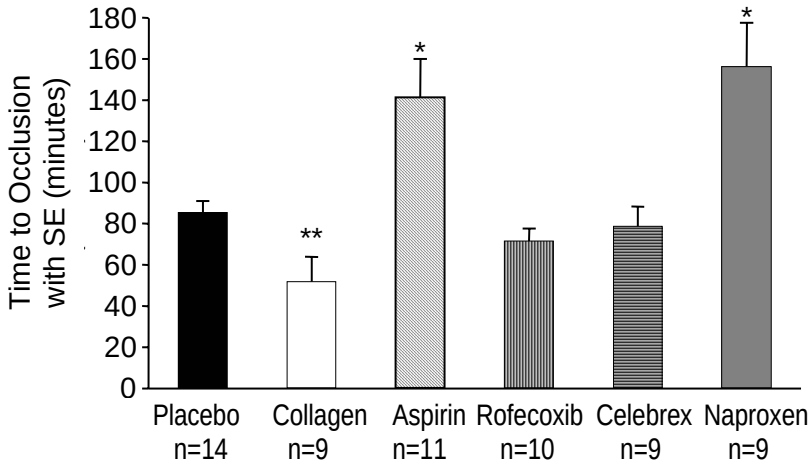
Thus, these data demonstrate a gradient of antiplatelet effects among the nonselective NSAIDs and rofecoxib, indicating that certain nonselective NSAIDs such as naproxen, with both potent and sustained antiplatelet effects might provide aspirin-like anti-platelet effects when appropriately dosed and used continuously. Similar results have been reported by other investigators [61] for the antiplatelet effects of naproxen, celecoxib, and valdecoxib [62].

Preclinical Data

Preclinical data consistent with naproxen having an antithrombotic effect come from studies in the African green monkey (Figure 22). In this model, animals exposed for 5 days to placebo, rofecoxib, celecoxib, naproxen, collagen, or aspirin were evaluated following electrolytic injury to the carotid artery and jugular vein. The aspirin arm was designed to be a positive control to represent effects of an antiplatelet agent. The collagen arm was designed to be a positive control to represent effects of a prothrombotic agent. COX-2 inhibition with either rofecoxib or celecoxib had no demonstrated effect on either arterial or venous thrombosis compared to placebo. Those treated with naproxen, however, demonstrated significantly prolonged times to both arterial and venous thrombosis compared to placebo. The time to thrombosis in the aspirin group had similar outcomes to naproxen; a significantly prolonged time to arterial thrombosis and a numerically increased time to venous thrombosis. The results of this study suggest that COX-2 inhibition has no effect on thrombosis and that naproxen exhibits antithrombotic effects similar to aspirin.

Figure 22

Time to Occlusion in Carotid Artery – African Green Monkey Model of Thrombosis



**p=0.06; Collagen < Placebo

*p<0.05; Aspirin & Naproxen > Placebo

Clinical Trials Evaluating the Vascular-Protective Properties of Nonselective NSAIDs

Although there have been no cardiovascular outcomes trials with naproxen, there is evidence for the vascular-protective efficacy of flurbiprofen and indobufen, two nonselective NSAIDs which exhibit potent antiplatelet properties. Flurbiprofen treatment has been shown to prolong bleeding time and was evaluated for a cardioprotective effect compared with placebo in the setting of coronary plaque rupture [63]. In this study, 464 patients who were successfully treated for acute myocardial infarction by thrombolysis and/or coronary angioplasty were randomized to receive either placebo or flurbiprofen 50 mg twice daily for 6 months. Use of aspirin or ticlopidine during the treatment period was not allowed. The primary endpoint was recurrent myocardial infarction or reocclusion of the infarct-related coronary artery. Therapy with flurbiprofen was associated with a >50% reduction in the incidence of reinfarction and coronary revascularization at 6 months [63] and a 71% reduction in the risk of myocardial infarction when compared with placebo treatment. The benefit was observed regardless of whether the patients underwent thrombolysis or percutaneous transluminal coronary angioplasty as therapy for the index myocardial infarction. This study specifically addressed the effects of flurbiprofen in the context of acute cardiovascular disease.

The data on the cardioprotective effects of the nonselective NSAID indobufen are even more compelling, although they are not as extensive as available for aspirin or clopidogrel. Clinical studies compared the effects of indobufen with placebo, aspirin, warfarin, or ticlopidine in patients with intermittent claudication resulting from peripheral vascular disease, in the prophylaxis of thromboembolism in patients with heart disease, in the prophylaxis of occlusion of coronary and femoropopliteal artery bypass grafts, and in the secondary prevention of thrombotic events following transient ischemic attack (TIA) and stroke [64; 65; 66; 67]. Collectively, these randomized double-blind clinical studies showed that indobufen treatment was associated with cardioprotective effects superior to placebo and similar to aspirin or warfarin although not as effective as ticlopidine.

When compared to placebo, indobufen therapy for 26 months was associated with a 65% reduction in the risk of a primary event (defined as fatal and nonfatal ischemic stroke and pulmonary embolism, fatal myocardial infarction and nonfatal systemic embolism and TIA) and reduced the risk of stroke 3-fold in patients with heart disease who were at risk of thromboembolism [66]. When evaluated for the prevention of saphenous vein graft occlusion in patients undergoing coronary artery bypass graft surgery indobufen therapy resulted in a significant reduction in the incidences of vein graft occlusion at 1 month and at 1 year, when compared with aspirin plus dipyridamole. When evaluated for the secondary prevention of thrombotic events in patients with nonrheumatic atrial fibrillation and a recent (<15 days) cerebral ischemic episode, no difference was noted for patients treated with indobufen versus warfarin over 1 year of treatment [67].

The data from these studies suggest that nonselective COX-1/COX-2 inhibitors with potent and sustained platelet COX-1 inhibitory properties result in vascular-protective properties similar to those observed with aspirin and the anticoagulant agent warfarin.

Clinical Trials Demonstrating a Difference in Cardiovascular Event Rates Between Naproxen and Other Selective COX-2 Inhibitors

Recent clinical data further suggest a difference in thrombotic cardiovascular events between selective COX-2 inhibitors and naproxen but not between selective COX-2 inhibitors and other non-selective NSAIDs. These include data from other COX-2 inhibitor programs under investigation, the largest single trial being the TARGET study with lumiracoxib [8].

The TARGET study, which enrolled over 18,000 patients, was designed to assess GI outcomes but a key secondary objective was to measure and compare a composite endpoint of cardiovascular morbidity and mortality. TARGET consisted of 2 substudies of equal size with one comparing lumiracoxib to ibuprofen 800 mg 3x daily and the other lumiracoxib to naproxen 500 mg 2x daily. In TARGET, the hazard ratio (95% CI) of confirmed or probable APTC events for lumiracoxib versus ibuprofen was 0.76 (0.41, 1.40) while the hazard ratio (95% CI) of confirmed or probable vascular APTC for lumiracoxib versus naproxen was 1.46 (0.89, 2.37). The differences between lumiracoxib and ibuprofen and between lumiracoxib and naproxen were not significant (p=0.3775 and p=0.1313, respectively), and the treatment-by-substudy interaction result was nonsignificant (p=0.1145). However, the TARGET study was not powered for the cardiovascular endpoint. The hazard ratio for the APTC combined endpoint in the lumiracoxib versus naproxen substudy is not inconsistent with the hypothesis that naproxen 500 mg twice daily has cardiovascular effects different from ibuprofen and lumiracoxib.

6.2 CV Adjudication Standard Operating Procedure (SOP)

To more precisely assess the CV safety profile of its selective COX-2 inhibitors, Merck initiated an Adjudication Standard Operating Procedure (CV Adjudication SOP) in the second half of 1998. The CV Adjudication SOP had been established due to emerging knowledge of the differences in antiplatelet effects among nonselective NSAIDs and in response to the theoretical implications of a thromboxane-prostacyclin imbalance with selective COX-2 inhibitors, as well as the theoretical potential for nonselective NSAIDs and or COX-2 inhibitors to be cardioprotective [68; 69]. The CV Adjudication SOP was initiated in the second half of 1998, prior to initiation of Phase IIb of the etoricoxib development program. The CV Adjudication SOP established a process by which potential thrombotic CV adverse experiences occurring in clinical trials of etoricoxib could be identified and adjudicated in a blinded manner, by external panels of experts in cardiovascular medicine in order to more precisely assess CV adverse experiences which occurred during the clinical development program. The analysis of CV outcomes in trials

of etoricoxib as described in the SOP was designed to examine the combined incidence of CV outcomes across a broad range of patients in all trials with chronic dosing (defined as studies with planned duration of at least 4 weeks); 12 studies met this criteria and were thus included.

Statistical Methods (Pooled Analysis)

The statistical approach outlined in the CV Adjudication SOP stipulated that patients receiving etoricoxib doses ≥60 mg would be combined into a single etoricoxib treatment group to increase statistical precision. Data from treatment periods on lower doses of etoricoxib (<60 mg) treatment were excluded as they do not represent maximally efficacious doses. As clinical trials data subsequently became available which established 30 mg as an effective dose for the symptomatic treatment of OA, post-hoc sensitivity analyses were performed which included the 30-mg dose experience in the combined etoricoxib group in the primary pooled analysis. Those data are not summarized in this document, but the results were consistent with the primary analysis which considered doses of etoricoxib ≥60 mg.

6.3 Definition of Cardiovascular Endpoints

The primary endpoint used in the pooled analysis for etoricoxib was Confirmed Thrombotic Cardiovascular serious adverse experiences. The Confirmed Thrombotic CV serious adverse experience endpoint represents the composite of all adverse experiences which were confirmed to be thrombotic based on the adjudication process and includes cardiac, cerebrovascular, and peripheral vascular events such as unstable angina, myocardial infarction, ischemic stroke and transient ischemic attacks, but does not include fatal hemorrhagic deaths or hemorrhagic stroke This endpoint was chosen as primary because it represents the largest amount of adjudicated data for etoricoxib, and thus allows for the most precise estimate of CV event rates. The Antiplatelet Trialists' Collaboration (APTC) combined endpoint was also evaluated. All deaths reported during etoricoxib clinical trials were also adjudicated. Table 4 outlines the different events included in the APTC combined endpoint and the Confirmed Thrombotic CV serious adverse experience endpoint.

An evaluation of thrombotic CV serious adverse experiences using the Confirmed Thrombotic CV endpoint is presented below based on data pooled from the etoricoxib development program. Thrombotic CV safety data from the EDGE study are presented separately, as this study is sufficiently large to provide an independent assessment of CV safety and will be combined with data from two other large studies in a prespecified analysis (see Section 8). Results for the APTC combined endpoint were consistent with results for the Confirmed Thrombotic CV serious adverse experience endpoint, but are not presented for purpose of brevity.

Table 4

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

Adjudication Committee Categories for Cardiovascular Events	Confirmed Thrombotic Cardiovascular Event	APTC† Combined 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‡		√
Fatal: hemorrhagic cerebrovascular stroke‡		√
Fatal: hemorrhagic deaths of any cause		√

† APTC = Antiplatelet Trialists' Collaboration.
‡ These events are included as investigator-reported events but not Confirmed Thrombotic CV serious adverse experiences.

6.4 Results

Results are summarized below for all currently available thrombotic CV safety data from the etoricoxib development program. This includes the prespecified pooled analysis of thrombotic CV safety data from all Phase IIb/III Chronic Exposure studies and from the EDGE study. In addition, results of a study which evaluated the effects of etoricoxib on established markers of CV risk are also briefly summarized.

6.4.1 Pooled Analysis of CV Data

The primary objective of the pooled analysis is to improve the precision of the estimate of CV event rates and relative risks for the development of a thrombotic CV event on etoricoxib versus comparator nonselective NSAIDs or placebo. The tabulation of thrombotic CV adverse experiences took into account the differing antiplatelet effects of comparator NSAIDs, specifically separating naproxen based on its potent and sustained antiplatelet effects [6; 7]. Additional rationale for keeping comparisons to naproxen separate from other NSAIDs includes results from the rofecoxib GI outcomes trial (VIGOR) showing a decreased risk for naproxen, heterogeneity encountered in trying to combine naproxen and non-naproxen NSAID data during the first pooled analysis of the rofecoxib data [70; 71], and the qualitative difference observed in the comparison of etoricoxib to naproxen vs. the comparison of etoricoxib to the other NSAIDs (ibuprofen and diclofenac combined). The data sets were thus defined in order to allow for the following comparisons: (1) placebo-controlled data set which compared etoricoxib to placebo, (2) non-naproxen-NSAID-controlled data set which compared etoricoxib to all NSAID comparators pooled other than naproxen (diclofenac, ibuprofen), (3) naproxen-controlled data set which compared etoricoxib to naproxen. In all three data sets, the etoricoxib group consisted of combined data for all etoricoxib doses of ≥60 mg. The rationale was to increase precision for comparisons to placebo and comparator NSAIDs. However, data are provided by dose, which in demonstrating no apparent etoricoxib dose effect, support this approach.

The pooled analysis consists of data from the Chronic Exposure studies, which include over 6700 patients representing approximately 6500 patient-years at risk. In these 12 studies, which are outlined in Table 5, a total of 124 serious adverse experiences in 116 patients were adjudicated. Of these, 74 Confirmed Thrombotic CV serious adverse experiences occurred in 69 patients.

Table 5

Studies Included in the Etoricoxib Pooled CV Analysis

Indication for Therapy	Protocol No.	Short Study Title	Comparator
Rheumatoid Arthritis	010	Phase IIb dose finding	Placebo, diclofenac
	024	Phase III pivotal U.S.	Placebo, naproxen
	025	Phase III pivotal Int'l	Placebo, naproxen
	026	Endoscopy	Placebo, naproxen
Osteoarthritis	007	Ph IIb dose ranging study	Placebo, diclofenac
	018	Ph III pivotal Int'l	Placebo, naproxen
	019	Ph III pivotal U.S.	Placebo, naproxen
	026	Endoscopy	Diclofenac
	029	Endoscopy	Ibuprofen, placebo
	805	Phase III Int'l	Diclofenac
Other	032	Ph III AS	Placebo, naproxen
	041	Ph III Chronic low back pain	Placebo
	042	Ph III Chronic low back pain	Placebo

Event rates (per 100 patient years) with 95% CIs and relative risks (with 95% CIs) for Confirmed Thrombotic CV serious adverse experiences for each data set are displayed in Table 6. The rates (per 100 patient years of exposure) are used to calculate the relative risks. KM plots for cumulative incidence rates of Confirmed Thrombotic CV serious adverse experiences for all 3 data sets are depicted in Figure 23.

In these KM plots the number of patients at risk displayed along the x-axis at a given point in time is representative of the number of patients remaining in the study at those time points. As the data sets are composed of several studies with differing durations, there is no way to accurately reflect the duration in a single value. The number of patients at risk indicated in the KM plot provide this type of information as they are reflective of the patient number and duration of therapy throughout the study. Kaplan-Meier estimates are imprecise when the number of patients remaining at risk is small at the end of the study and it is recommended that the plot be curtailed when approximately 10 to 20% of patients remain in follow-up [72]. This approach was generally followed; Kaplan-Meier curves were truncated when there were around 10 to 20% of patients remaining at risk in any treatment group (or ~150-200 patients). Such a truncation was just for the plot; any events occurring after the truncation time point were still retained in the analyses of crude proportions, patient-year adjusted incidence rates and relative risks and also displayed in the relevant tables.

In these data, the ability to precisely estimate the magnitude of the difference between treatment groups remains limited given the relatively small numbers of events, as reflected in the width of the 95% CIs.

Placebo-Controlled Data Set

Table 6 shows the comparison of etoricoxib to placebo for Confirmed Thrombotic CV serious adverse experiences. The relative risk (95% CI) for etoricoxib is 1.11 (0.32, 3.81). These data, although limited, support that there is no evidence of a discernible difference between etoricoxib and placebo. These data extend to 12 weeks of therapy as there is no placebo-controlled data beyond this time interval.

Non-Naproxen NSAID-Controlled Data Set

Table 6 shows the comparison of etoricoxib to non-naproxen NSAIDs for Confirmed Thrombotic CV serious adverse experiences. The relative risk (95% CI) for etoricoxib is 0.83 (0.26, 2.64). Based on these data, there is no evidence to support a discernible difference between etoricoxib and non-naproxen NSAIDs for Confirmed Thrombotic CV adverse experiences.

Naproxen-Controlled Data Set

Table 6 shows a comparison of etoricoxib to naproxen for Confirmed Thrombotic CV serious adverse experiences. The relative risk (95% CI) for etoricoxib is 1.70 (0.91, 3.18). These results suggest a difference between treatment groups in Confirmed Thrombotic CV serious adverse experiences with a decreased risk for naproxen.

Although the 95% CI for the relative risk includes 1 for the comparison between etoricoxib and naproxen, this likely represents a real difference given the contrast in the point estimates for the relative risk compared to the results from the placebo and non-naproxen-controlled data sets.

Overall, the results for the APTC combined endpoint were generally consistent with those of the Confirmed Thrombotic CV serious adverse experience endpoint and support the conclusion of no discernible difference between etoricoxib and placebo or etoricoxib and non-naproxen NSAIDs. These data do suggest that a true difference is likely between etoricoxib and naproxen.

Table 6

Absolute Rate and Relative Risk (95% CI)
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
Pooled CV Analysis

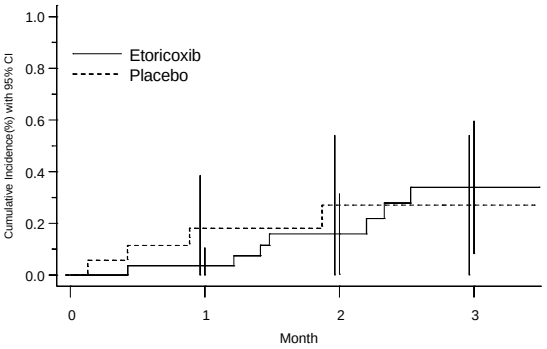
Comparisons	N	Cases/PYR[†]	Rate[‡] (95% CI)	Relative Risk[§] (95% CI)
Confirmed Thrombotic Cardiovascular Adverse Experiences				
Etoricoxib[‖]	2818	7/560	1.25 (0.50, 2.58)	1.11 (0.32, 3.81)
Placebo	1767	4/335	1.19 (0.33, 3.06)	--
Etoricoxib	1266	12/1522	0.79 (0.41, 1.38)	0.83 (0.26, 2.64)
Non-Naproxen 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)	--

† 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.
‖ ≥60 mg etoricoxib
¶ Ibuprofen and diclofenac
APTC = Antiplatelet Trialists' Collaboration; CI = Confidence interval; PYR = Patient-years at risk.

Figure 23

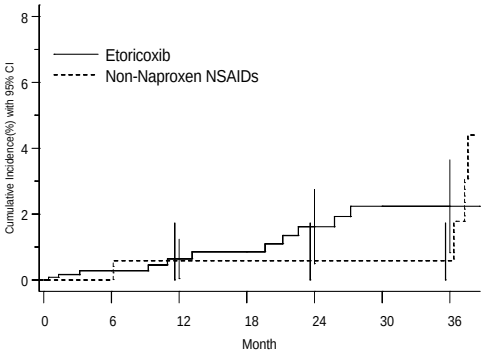
Kaplan-Meier Estimates of Cumulative Incidence of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
Pooled CV Analysis by Data Set

Placebo-Controlled Data Set†



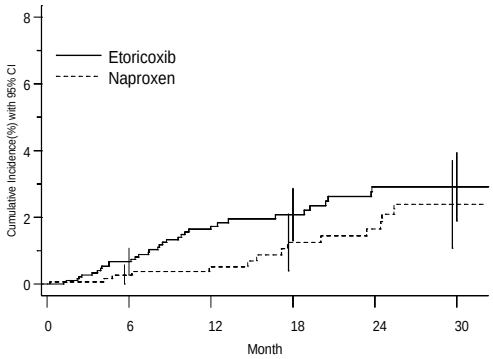
# Patients at Risk				
Etoricoxib	2818	2625	1710	801
Placebo	1767	1435	1074	607

Non-Naproxen NSAID Controlled Data Set‡



# Patients at Risk							
Etoricoxib	1266	604	524	415	352	295	236
lon-Naproxen NSAIDs	718	174	133	116	94	85	83

Naproxen-Controlled Data Set†



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

† 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 ± 95% CIs of cumulative incidence (%) at the indicated time points.
Plots were truncated when the risk size in any arm is <50.

All Confirmed Thrombotic CV serious adverse experiences were categorized by the CV adjudication committee by category (cardiac, cerebrovascular, or peripheral vascular) and by specific event type. Table 7, Table 8, and Table 9 summarize the Confirmed Thrombotic CV serious adverse experiences by category and treatment group for the Placebo-Controlled, Non-Naproxen-NSAID, and Naproxen-Controlled Data Sets, respectively. In these 3 tables, the CV events are also expressed as a percent of the total number of patients exposed in the respective treatment groups which does not take into account patient-years of exposure. The rates per 100 patient years of exposure are also displayed.

Overall, there is no clear pattern to the specific thrombotic CV adverse experiences. In all 3 data sets, CV adverse experiences are generally reported in all 3 vascular beds, with more cardiac events than cerebrovascular or peripheral vascular events regardless of treatment group. In considering the difference between the naproxen and etoricoxib groups, no single type of adverse experience predominates, although a higher incidence of ischemic cerebrovascular stroke was observed with etoricoxib compared to naproxen (Table 9). No peripheral vascular events occurred in the Non-Naproxen-NSAID Controlled data set as summarized in Table 8.

Table 7

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

	Etoricoxib (N=2818)		Placebo (N=1767)	
	(PYR=560)		(PYR=335)	
Endpoint Terms	n (%)[†]	Rate[‡]	n (%)[†]	Rate[‡]
Patients With One or More Confirmed Thrombotic Cardiovascular 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
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
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

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

Table 8

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

	Etoricoxib (N=1266)		Non-Naproxen NSAIDs					
			Combined (N=718)		Diclofenac (N=492)		Ibuprofen (N=226)	
	(PYR=1522)		(PYR=501)		(PYR=447)		(PYR=54)	
Endpoint Terms	n (%)[†]	Rate[‡]	N (%)[†]	Rate[‡]	n (%)[†]	Rate[‡]	n (%)[†]	Rate[‡]
Patients With One or More Confirmed Thrombotic Cardiovascular 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

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

Table 9

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

	Etoricoxib (N=1960)		Naproxen (N=1497)	
	(PYR=2480)		(PYR=1727)	
Endpoint Terms	n (%)[†]	Rate[‡]	n (%)[†]	Rate[‡]
Patients With One or More Confirmed Thrombotic Cardiovascular 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
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
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

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

Analyses of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in Patients With and Without Antecedent Hypertension-Related Adverse Experiences

Patients with hypertension are at increased risk for cardiac and cerebrovascular disease and these effects are generally seen following long-standing and under-treated hypertensive disease [73]. Although the renovascular effects of etoricoxib are generally similar to comparator NSAIDs (Section 5) and the time period encompassed by these studies is relatively short in relation to the time it generally takes to manifest the CV sequelae of under-treated hypertension, analyses were performed to explore the relationship between study treatment effects on blood pressure and Confirmed Thrombotic CV adverse experiences.

Specifically, the incidence rates of Confirmed Thrombotic CV serious adverse experiences were compared in patients with and without an antecedent hypertension-related adverse experience within the Naproxen-Controlled data set by treatment group (Table 10). This data set was evaluated as it was the only data set in which a difference between treatment groups was observed for Confirmed Thrombotic CV serious adverse experiences, thus the potential effect of blood pressure was explored. The overall difference in Confirmed Thrombotic CV serious adverse experience rates between etoricoxib and naproxen appeared to be observed in patients without antecedent hypertension-related adverse experiences. An additional analysis compared the incidence rates of antecedent hypertension-related adverse experiences in patients with Confirmed Thrombotic CV serious adverse experiences (Table 11) and showed the incidence of antecedent hypertension was generally similar in patients with and without a Confirmed Thrombotic CV serious adverse experience, particularly in patients treated with etoricoxib. These analyses support the observation that the difference in the incidence of Confirmed Thrombotic CV serious adverse experiences between etoricoxib and naproxen cannot be explained by between-group differences in effects on blood pressure as characterized by hypertension adverse experiences.

Table 10

Incidence of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences in Patients With and Without Antecedent Hypertension-Related Adverse Experiences
Naproxen-Controlled Data Set

Subgroup	Treatment Group	N	Patients With a Confirmed Thrombotic Event	
			n	(%)
Incidence of a Confirmed Thrombotic Cardiovascular Adverse Experience				
Patients with a hypertension-related adverse experience before the thrombotic event	Etoricoxib†	237	3	(1.3)
Patients without a hypertension-related adverse experience before the thrombotic event	Etoricoxib†	1723	31	(1.8)
Patients with a hypertension-related adverse experience before the thrombotic event	Naproxen 1000 mg	129	2	(1.6)
Patients without a hypertension-related adverse experience before the thrombotic event	Naproxen 1000 mg	1368	12	(0.9)
† ≥60 mg etoricoxib.				

Table 11

Incidence of Antecedent Hypertension-Related Adverse Experiences in Patients With and Without Confirmed Thrombotic Cardiovascular Serious Adverse Experiences Naproxen-Controlled Data Set

Subgroup	Treatment Group	N	Patients With an Antecedent Hypertension-Related Adverse Experience	
			n	(%)
Incidence of an Antecedent Hypertension-Related Adverse Experience				
Patients with a confirmed thrombotic cardiovascular adverse experience	Etoricoxib†	34	3	(8.8)
Patients without a confirmed thrombotic cardiovascular adverse experience	Etoricoxib†	1926	234	(12.1)
Patients with a confirmed thrombotic cardiovascular adverse experience	Naproxen 1000 mg	14	2	(14.3)
Patients without a confirmed thrombotic cardiovascular adverse experience	Naproxen 1000 mg	1483	127	(8.6)

† ≥60 mg etoricoxib.

Analysis by Disease Indication

Confirmed Thrombotic CV serious adverse experiences were analyzed by disease indication (OA, RA) using the Naproxen-Controlled data set, since this is the largest data set and thus the most suitable for subgroup analysis. In this data set, the OA and the RA populations both included two Phase III studies and the relevant portion of data from the Phase III OA/RA surveillance endoscopy study. Analyses are presented for the Confirmed Thrombotic CV serious adverse experiences.

Table 12 summarizes the relative risk for etoricoxib versus naproxen in OA and RA patients for Confirmed Thrombotic CV adverse experiences. The relative risks were similar for OA and RA patients, and the treatment-by-subgroup disease interaction was not significant (p-value >0.82). These data indicate that the magnitude of the difference between etoricoxib and naproxen is similar between these two disease states and not increased in RA patients.

Table 12

Absolute Rate and Relative Risk (95% CI)
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
by Disease Type (OA, RA)
Naproxen-Controlled Data Set

Disease, Treatment	N	Cases/PYR	Rate[†] (95% CI)	Relative Risk[‡] (95% CI)
Confirmed Thrombotic Cardiovascular Adverse Experiences[§]				
Total Cohort				
Etoricoxib[‖]	1960	34/2480	1.37 (0.95, 1.92)	1.70 (0.91, 3.18)
Naproxen	1497	14/1727	0.81 (0.44, 1.36)	-
OA Studies only				
Etoricoxib[‖]	558	11/742	1.48 (0.74, 2.65)	1.66 (0.61, 4.49)
Naproxen	531	6/671	0.89 (0.33, 1.95)	-
RA Studies only				
Etoricoxib[‖]	1149	18/1522	1.18 (0.70, 1.87)	1.41 (0.61, 3.25)
Naproxen	839	8/953	0.84 (0.36, 1.65)	-

[†] Per 100 patient-years at risk.
[‡] Relative risk to naproxen using Cox model where the number of cases is at least 11; otherwise, the relative risk is the ratio of rates.
[§] Treatment by subgroup interaction non significant.
[‖] Etoricoxib ≥60 mg.
Total Cohort = OA + RA + Ankylosing Spondylitis
N=Total number of patients; CI=Confidence Interval; PYR=Patient-Years at Risk.

As indicated previously, the total cohort includes data from a single AS study. This was a two-part, double-blind study, with treatment assignment for both parts established prior to randomization. In Part I (6 weeks in duration), patients were randomized to placebo (n=93), etoricoxib 90 mg once daily (n=103), etoricoxib 120 mg once daily (n=92), or naproxen 500 mg twice daily (n=99). In Part II (46 weeks in duration), patients assigned to placebo in Part I were reassigned to 1 of the 3 active treatment groups, resulting in the following Part II treatment group sizes: etoricoxib 90 mg (n=126), etoricoxib 120 mg (n=123), or naproxen 500 mg twice daily (n=125). There were a total of 5 Confirmed Thrombotic CV adverse experiences in this study; 4 events occurred in the etoricoxib 90-mg group (1 acute myocardial infarction, 1 ischemic stroke, 2 patients with unstable angina), and 1 event in the etoricoxib 120-mg group (1 ischemic stroke). The rate of confirmed thrombotic events in this study did not differ substantially from what would have been predicted based on the rates observed in the Naproxen-Controlled Data Set from the pooled analysis.

Analysis by Dose

Thrombotic CV event rates by dose of etoricoxib were evaluated by analyzing event rates by dose across all studies included in the CV pooled analysis using two different analytical approaches.

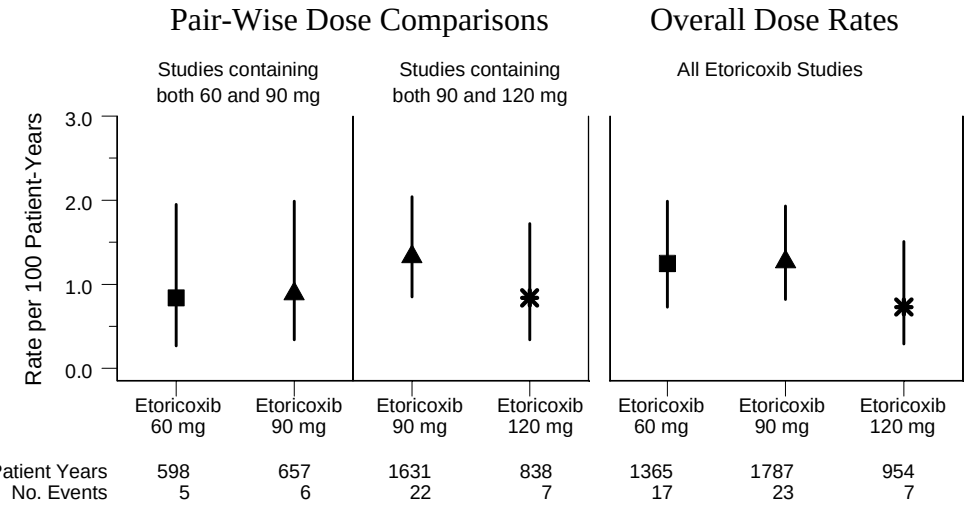
The primary approach, referred to as a pair-wise analysis, is based on a dose analysis which includes data only from those studies which contained both doses being analyzed (i.e., both 60 and 90 mg or both 90 and 120 mg). As only one study (a phase II OA study) contained 60, 90, and 120 mg doses of etoricoxib, a pair-wise analysis was done by combining studies that contained both the 60- and 90-mg dose groups and studies containing both the 90- and 120-mg dose groups.

A secondary analysis includes rates by individual doses (60, 90, and 120 mg) combined across all of the studies included in the CV pooled analysis. While this approach is more comprehensive, it must be interpreted cautiously because doses are partially confounded by differences across protocols. As a result, differences in patient populations between the doses being compared can affect the analysis.

The rates per 100 patient-years (95% CI) for the primary pair-wise analysis for Confirmed Thrombotic CV serious adverse experiences are displayed in Figure 24. The estimated rates for Confirmed Thrombotic CV serious adverse experiences for etoricoxib 60 mg were generally similar to 90 mg. The estimated rates for etoricoxib 90 mg were similar to 120 mg. The rates per 100 patient-years (95% CI) for the secondary analysis of dose across all studies for the Confirmed Thrombotic CV serious adverse experiences endpoint were consistent with the analyses provided above, and provide no evidence of a dose-related effect across the 60- to 120-mg dose range of etoricoxib.

Figure 24

Rates Per 100-Patient Years (95% CIs) of Confirmed Thrombotic Cardiovascular Serious Adverse Experiences Stratified by Etoricoxib Dose
Pooled CV Analysis



Analysis by CV Risk Factor and Aspirin Use

In order to further evaluate the thrombotic cardiovascular safety of etoricoxib, post-hoc subgroup analyses were performed on patient cohorts known to be at increased baseline cardiovascular risk. Two subgroups were identified which met this criteria. The first of these analyses included patients at increased baseline risk, defined as having 2 or more of 4 primary cardiac risk factors (i.e., tobacco use, diabetes mellitus, hypertension, or hypercholesterolemia), or a history of symptomatic atherosclerotic cardiovascular disease (ASCVD) (specifically, myocardial infarction, angina pectoris, cerebral vascular accident, transient ischemic attack, angioplasty, or coronary artery bypass surgery). The second subgroup was defined as patients on anti-platelet therapy for cardioprophylaxis, indicating a subgroup of patients presumably largely with existing CV disease and thus at increased risk for a recurrent event. For this analysis, a patient on anti-platelet therapy was defined as anyone who took any dose of aspirin, clopidogrel, clopidogrel bisulfate, ticlopidine, or ticlopidine hydrochloride for at least 50% of the time while on study therapy. There was very limited use of concomitant antiplatelet therapies in these studies (5.2%), the majority of which was aspirin, hence this subgroup is referred to as aspirin users. Thus, the data comparing the CV safety of etoricoxib to naproxen in subgroups of aspirin users versus nonusers are limited and should be interpreted with caution. Additional CV safety data in the presence and absence of aspirin use, from the EDGE study are presented in Section 6.4.2.

For etoricoxib, these analyses were performed on the Naproxen-Controlled data set, since this is the largest data set. The rates and 95% CI for the Confirmed Thrombotic CV serious adverse experiences for the Naproxen-Controlled data set by baseline CV risk and by aspirin use are provided in Table 13.

The difference observed in the total cohort between naproxen and etoricoxib was generally observed in both the increased-risk and the not-increased-risk patient subgroups. Treatment by subgroup interaction analyses indicated the observed differences between increased-risk and not-increased-risk subgroups in Confirmed Thrombotic CV serious adverse experiences were not significant (p-value=0.81), indicating no discernible evidence of a different relative risk associated with etoricoxib versus naproxen for patients at increased CV risk in comparison to patients not at increased CV risk.

In the limited data for the cohort of aspirin users, no firm conclusions can be drawn, although the following observations can be made. The event rates were overall higher in the cohort of aspirin users, consistent with the notion that aspirin users were presumably taking aspirin to mitigate a higher underlying CV risk. The event rates were similar between etoricoxib and naproxen in the cohort of aspirin users, whereas the event rates are different between etoricoxib and naproxen in the cohort of non-aspirin users. This is consistent with the hypothesis that antiplatelet effects of naproxen can confer a difference in CV event rates between etoricoxib and naproxen but is based on a limited dataset and treatment-by-subgroup interaction analyses indicated the differences in Confirmed Thrombotic CV serious adverse experiences observed between aspirin users and non-users were not significant (p-value=0.57).

Table 13

Absolute Rate and Relative Risk (95% CI)
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
Subgroup Analysis by Baseline Cardiovascular Risk and Aspirin Use
Naproxen-Controlled Data Set

Subgroup	Treatment	n/N (%)	Patient-Years	Rate[†] (95% CI[‡])
Cardiovascular Risk				
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)
Increased risk[§]	Etoricoxib	15/359 (4.18)	450	3.33 (1.87, 5.50)
	Naproxen	6/287 (2.09)	341	1.76 (0.65, 3.83)
Not increased risk	Etoricoxib	19/1601 (1.19)	2030	0.94 (0.56, 1.46)
	Naproxen	8/1210 (0.66)	1387	0.58 (0.25, 1.14)
Aspirin Users[‖]				
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.
[§] 2 or more cardiovascular risk factors for coronary artery disease (history of diabetes, hypercholesterolemia, hypertension, and tobacco use) or a history of symptomatic atherosclerotic cardiovascular disease
[‖] 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.
n/N=the number of patients with events/total number of patients; CI=Confidence Interval.

6.4.2 EDGE Study CV Data

This section provides a summary of the CV safety results from the EDGE study. This study serves as an independent database to the pooled analysis data and thus provides an opportunity to confirm results observed in the pooled analysis.

The EDGE study included 7111 patients, representing ~5400 patient-years at risk for the CV analysis. The prespecified primary endpoint for this analysis was the same as for the pooled analysis–Confirmed Thrombotic CV serious adverse experiences occurring on study therapy or within 14 days of discontinuing study therapy. In addition, all patients were contacted to assess for serious adverse experiences 28 days following the last dose of study therapy and through the end of the study for potential thrombotic CV serious adverse experiences to support an all-patients-treated analysis.

The primary analysis is based on 68 confirmed thrombotic adverse experiences in 65 patients (three patients had more than one adverse experience within the specified period, yielding a total of 65 patients with adverse experiences in the analyses). These data are summarized in Table 14. There were 35 patients in the etoricoxib group and 30 in the diclofenac group with Confirmed Thrombotic CV serious adverse experiences, resulting in rates of 1.25 and 1.15 per 100 patient-years, respectively, with a relative risk (95% CI) of 1.07 (0.65 to 1.74). A Kaplan-Meier plot for the cumulative incidence rates of Confirmed Thrombotic CV serious adverse experiences is depicted in Figure 25. Results for events occurring on therapy or within 28 days following discontinuation of study therapy (as requested by the FDA), as well as all events regardless of time were similar among the two treatment groups and thus consistent with the results of the primary endpoint (i.e., events occurring on therapy or within 14 days of study discontinuation). Results for the APTC events were generally similar to those of Confirmed Thrombotic CV serious adverse experiences (Figure 26).

Table 14

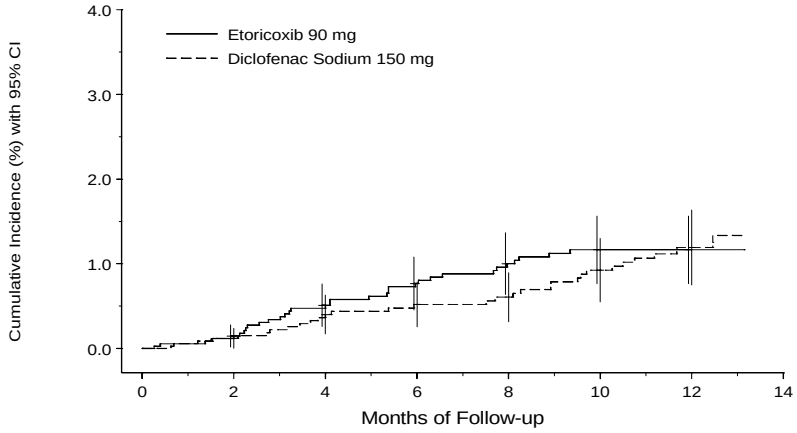
Absolute Rate and Relative Risk (95% CI)
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
The EDGE Study

Treatment	N	n/PYR[†]	Rate[‡] (95% CI)	Relative Risk (95% CI)
Events on therapy or within 14 days after study therapy discontinuation				
Etoricoxib 90 mg	3593	35 / 2789	1.25 (0.87 , 1.74)	1.07 (0.65 , 1.74)
Diclofenac Sodium 150 mg	3518	30 / 2607	1.15 (0.78 , 1.64)	
Events on therapy or within 28 days after study therapy discontinuation				
Etoricoxib 90 mg	3593	38/2926	1.30 (0.92 , 1.78)	1.02 (0.64 , 1.62)
Diclofenac Sodium 150 mg	3518	34/2740	1.24 (0.86 , 1.73)	
All Events				
Etoricoxib 90 mg	3593	41 /2927	1.40 (1.01 , 1.90)	1.01 (0.65, 1.58)
Diclofenac Sodium 150 mg	3518	37 / 2742	1.35 (0.95 , 1.86)	

[†] Patient-years at risk.
[‡] Per 100 PYR.

Figure 25

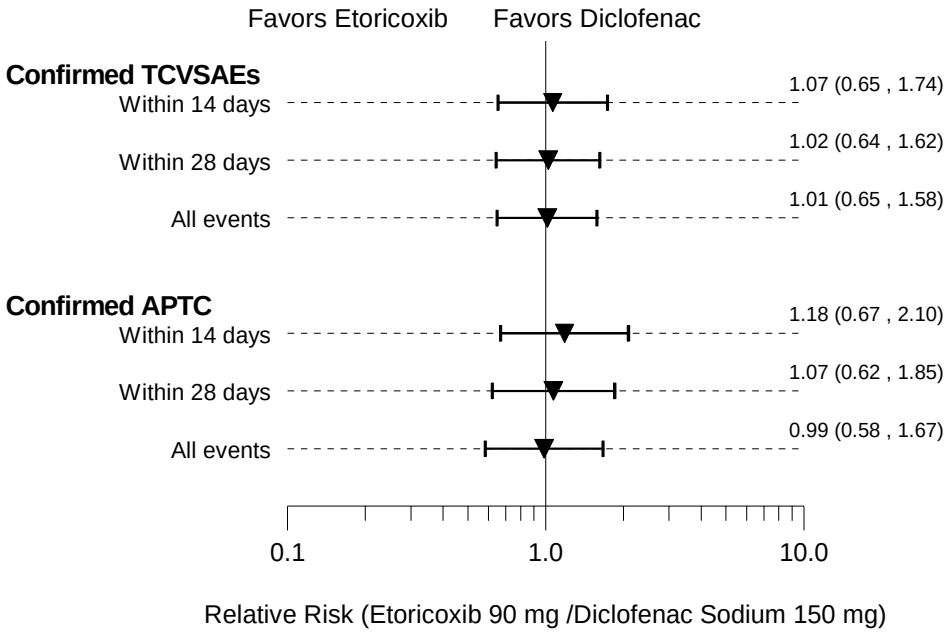
Kaplan-Meier Estimates of Cumulative Incidence of
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
(Events on Therapy or Within 14 Days after Study Therapy Discontinuation)
The EDGE Study



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

Figure 26

Relative Risk (95% CIs)
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences and
APTC Combined Endpoints
The EDGE Study



Spacing of x-axis is in logarithmic scale.
Confirmed TCVSAEs = Confirmed Thrombotic Cardiovascular serious adverse experiences

Table 15 summarizes the Confirmed Thrombotic CV serious adverse experience with rates per 100 patient-years of exposure by event category and treatment group occurring on therapy or within 14 days after study therapy discontinuation. Evaluation of individual events indicates small numeric differences between treatments for certain event types; some occurring at a higher rate on etoricoxib and some occurring at a lower rate, as expected for two treatments with similar overall rates. Specifically, small numeric differences favoring etoricoxib were observed for confirmed ischemic cerebrovascular stroke, whereas small numeric differences favoring diclofenac were observed for confirmed acute myocardial infarctions. None of these differences were statistically significant. The absolute number of any of these individual events was small, and results at the level of individual events cannot be appropriately interpreted further.

Table 15

Summary of Patients With Confirmed Thrombotic Cardiovascular
Serious Adverse Experiences by Class of Terms
(Events on Therapy or Within 14 Days after Study Therapy Discontinuation)
The EDGE Study

	Etoricoxib 90 mg (N=3593) 2789 Patient-Years		**Diclofenac Sodium 150 mg (N=3518) 2607 Patient-Years**	
Confirmed Adjudicated Event	**n (%)[†]**	**Rate[‡]**	**n (%)[†]**	**Rate[‡]**
Total number of patients with Endpoint	35 (0.97)	1.25	30 (0.85)	1.15
Cardiac Events	27 (0.75)	0.97	19 (0.54)	0.73
Acute myocardial infarction	19 (0.53)	0.68	11 (0.31)	0.42
Sudden cardiac death	2 (0.06)	0.07	1 (0.03)	0.04
Unstable angina pectoris	6 (0.17)	0.22	7 (0.20)	0.27
Cerebrovascular Events	7 (0.19)	0.25	7 (0.20)	0.27
Fatal ischemic cerebrovascular stroke	1 (0.03)	0.04	0 (0.00)	0.00
Ischemic cerebrovascular stroke	3 (0.08)	0.11	6 (0.17)	0.23
Transient ischemic attack	3 (0.08)	0.11	2 (0.06)	0.08
Peripheral Vascular Events	3 (0.08)	0.11	4 (0.11)	0.15
Peripheral arterial thrombosis	0 (0.00)	0.00	1 (0.03)	0.04
Peripheral venous thrombosis	2 (0.06)	0.07	0 (0.00)	0.00
Pulmonary embolism	1 (0.03)	0.04	3 (0.09)	0.12

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.

At the request of the FDA, an additional assessment was performed to include thrombotic CV serious adverse experiences occurring within 28 days after study therapy discontinuation. When results from this analysis were compared with those for events which occurred within 14 days following discontinuation of study therapy, overall differences between the treatment groups narrowed (rate per 100 patient years of 1.30 and 1.24 for etoricoxib and diclofenac, respectively; yielding relative risk [95% CI] of 1.02 [0.64, 1.62]). This appears to be due to a slight rate increase in the diclofenac group (rate per 100 patient years of 1.15 and 1.24 for within 14 days and 28 days, respectively), driven by a numeric increase in the rate of confirmed acute myocardial infarctions in the diclofenac group (rate per 100 patient-years of 0.42 and 0.51 for within 14 days and 28 days, respectively).

Analysis by Risk Factor

In order to further evaluate the thrombotic CV safety of etoricoxib, post-hoc subgroup analyses were performed on patient cohorts known to be at increased CV risk. Two subgroups previously defined for the pooled analysis were analyzed. Patients with an increased CV risk are defined as having 2 or more cardiac risk factors (a history of diabetes, hypercholesterolemia, hypertension, a family history of cardiovascular disease, or tobacco use) or a history of symptomatic ASCVD. Information on family cardiac history was not available for the studies included in the pooled CV analysis; however, these data were collected in the EDGE study and therefore were included. The rates and 95% CIs for the Confirmed Thrombotic CV serious adverse experiences on therapy or within 14 days after therapy discontinuation by baseline CV risk and baseline aspirin use are provided in Table 16.

As expected, absolute event rates were higher in the increased-risk subgroup for both treatments. However, consistent with the overall results, no difference was observed between etoricoxib and diclofenac in both the increased-risk and the not-increased-risk patient subgroups. Treatment-by-subgroup interaction analyses showed no significant difference in Confirmed Thrombotic CV serious adverse experiences (p-value=0.31), indicating no important departure from similarity of treatment effects across subgroups. Results for the aspirin use analysis were also consistent with the overall results, showing similar rates for etoricoxib and diclofenac in both the aspirin user and non-user subgroups. Treatment-by-subgroup interaction analyses for aspirin users versus non-users indicated no difference in Confirmed Thrombotic CV serious adverse experiences (p-value=0.81).

Table 16

Absolute Rate and Relative Risk (95% CI)
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
Subgroup Analyses by Baseline Cardiovascular Risk and Aspirin Use
(Events on Therapy or Within 14 Days After Study Therapy Discontinuation)
The EDGE Study

Subgroup	Treatment	n/N (%)	Rate[†]	Relative Risk (95%)
Cardiovascular Risk				
Increased Risk[‡]	Etoricoxib Diclofenac	20/1335 (1.50) 21/1345 (1.56)	1.94 2.11	0.92 (0.50, 1.69)
Not Increased Risk	Etoricoxib Diclofenac	15/2258 (0.66) 9/2173 (0.41)	0.85 0.56	1.49 (0.65, 3.41)
Aspirin User[§]				
Aspirin User	Etoricoxib Diclofenac	17/1039 (1.64) 13/970 (1.34)	2.07 1.88	1.10 (0.53, 2.27)
Not Aspirin User	Etoricoxib Diclofenac	18/2554 (0.70) 17/2548 (0.68)	0.91 0.89	1.03 (0.53, 2.00)

n/N = the number of patients with events/total number of patients; CI = Confidence Interval.
[†] Number of events per 100 patient-years.
[‡] 2 or more cardiovascular risk factors for coronary artery disease (history of diabetes, hypercholesterolemia, hypertension, and tobacco use) or a history of symptomatic atherosclerotic cardiovascular disease.
[§] 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.

6.4.3 Cardiovascular Biomarker Data

The CV biomarker study compared the effects of placebo, etoricoxib 90 mg, celecoxib 400 mg, and ibuprofen 2400 mg on the levels of low-density lipoprotein cholesterol (LDL-C), homocysteine, fibrinogen, and C-reactive protein (CRP) in patients with OA after 3 months of treatment. The results of this study showed that treatment with etoricoxib 90 mg did not adversely affect LDL-C, homocysteine, fibrinogen, or CRP in patients with OA and in this study, etoricoxib was found to be noninferior to placebo, celecoxib, and ibuprofen for all biomarkers tested. In the comparisons with placebo at month 3, the observed effect of etoricoxib was numerically favorable in each case, albeit not statistically superior.

In this study, there was 1 event in 1 patient in the celecoxib treatment group that was adjudicated as a confirmed thrombotic event of acute myocardial infarction. There were no additional thrombotic CV serious adverse events (confirmed, or unconfirmed) in the placebo, etoricoxib, or ibuprofen treatment groups.

6.5 Postmarketing Cardiovascular Data

Postmarketing surveillance is an important signal detection tool after a new drug enters the market. The first suspicion of rare and non-mechanism based adverse experiences not detected in clinical trials usually arises from spontaneous reporting systems. For common adverse experiences (i.e. coronary heart disease), however, the background rate (640 to 1,100 per 100,000 patient-years of exposure in the U.S.) often is so much higher than the reported rate (3.5 per 100,000 patient-years of exposure worldwide, market introduction through 30-September-2004; Health Care Provider reports) that no conclusion of an association or an increased risk can be drawn. Similarly, mechanism-based adverse experiences from NSAID use (i.e. fluid retention and hypertension) are expected to occur and therefore are not systematically reported by health care practitioners for drugs of the same class; hence, no conclusions can be drawn regarding the magnitude of risk. Therefore, it is generally accepted that post marketing surveillance cannot be used to evaluate such adverse experiences, which only can be studied in clinical trials and/or observational studies.

It is also generally accepted that spontaneous reporting systems can only produce signals of potential cause–effect relationships because the information is most often incomplete and the systems are sensitive to multiple biases like time on market—reporting highest during the first years, media attention – leading to increased reporting, channeling high risk patients to new treatments etc. For irreversible effects it is impossible to make valid causal inference from spontaneous reports since two important criteria for causality evaluation—dechallenge and rechallenge are not applicable. Typical examples of such effects are CV events like thromboembolism including acute myocardial infarctions and cerebrovascular events. Such events can therefore only be evaluated in formal studies where the risk of the outcome is compared between exposed and non-exposed. Furthermore, spontaneous reports cannot be used to compare the risk of one type of adverse experience between different drugs, a fact recognized by the FDA and other experts.

Cardiovascular Events

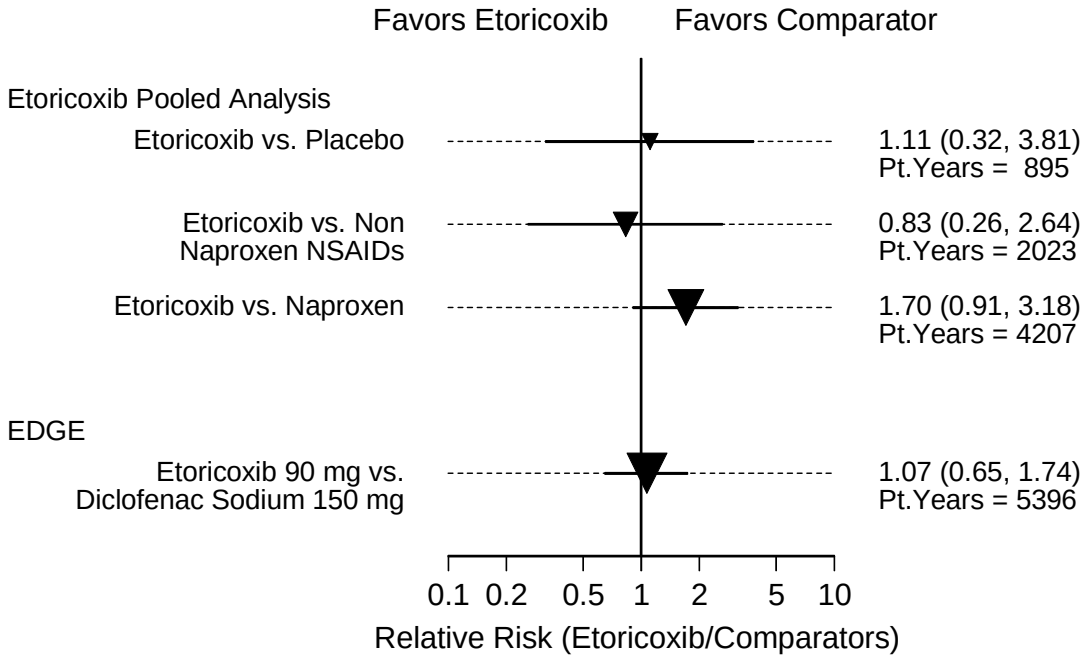
Based on an estimated total exposure of approximately 804,000 patient-years of treatment worldwide from market introduction through 30-Sep-2004, the 47 spontaneous reports of CV events identified in the Worldwide Adverse Experience System (WAES) database represent an overall reporting rate of 5.8 CV events per 100,000 patient-years of exposure. The overall reporting rates for cerebrovascular accident (CVA), coronary artery disease (CAD) and other thromboembolic events were 1.5, 3.7, and 0.6 per 100,000 patient-years of exposure, respectively. Preferred terms identified in the WAES database search included: CVA, transient ischemic attack, cerebral infarction, myocardial infarction, acute myocardial infarction, myocardial ischemia, angina pectoris, myocardial rupture, coronary artery disease, unstable angina, embolism, thrombosis, deep vein thrombosis, and ischemia. These rates are significantly less than those observed in randomized, controlled clinical trials, reflecting the limitation of these data due to under reporting.

6.6 CV Safety Summary and Conclusions

The results from the pooled analysis and the EDGE study are summarized in Figure 27 for the Confirmed Thrombotic CV adverse experience endpoint using a standard relative risk plot. The triangle represents the point estimate of the relative risk, with the size of the triangle proportional to the number of patient years included in the analysis. When comparing etoricoxib either to placebo or to non-naproxen-NSAIDs, there is no evidence of a discernible difference in event rates. When comparing etoricoxib to naproxen, a lower event rate is observed with naproxen, suggesting a true difference in event rates is likely between these 2 groups. The overall difference between the naproxen and etoricoxib groups was contributed to by events in the cardiac and cerebrovascular beds.

Figure 27

Relative Risk (95% CIs)
Confirmed Thrombotic Cardiovascular Serious Adverse Experiences
Pooled CV Analysis and the EDGE Study



Spacing of x-axis is in logarithmic scale.

Based on the evaluation of data from studies of at least 4 weeks in duration and adjudicated by expert committee blinded to the data:

- There is no evidence of a discernible difference in event rates among patients taking etoricoxib, placebo, or NSAIDs which lack potent and sustained antiplatelet activity. Limitations of these observations include the duration of the placebo-controlled data (data do not exceed 12 weeks in duration) and the quantity of longer term active comparator CV data.
- Naproxen 500 mg twice daily is associated with an incidence of thrombotic CV adverse experiences which is lower than that observed with etoricoxib. The difference is observed shortly after initiation of therapy.
- There is no discernible evidence of a dose-related effect in thrombotic CV adverse experiences.
- Evaluation of the data failed to identify any specific patient subgroup at increased relative risk for a thrombotic CV serious adverse experience, including RA patients and patients at increased baseline risk for a CV event.
- Data from the EDGE study are consistent with the Non-Naproxen-NSAID-Controlled Data Set in showing no evidence of a difference between etoricoxib and diclofenac in CV adverse experiences.

7. Mortality

A total of 28 patients died in the etoricoxib development program (excluding EDGE which is presented separately), either while taking study medication, or within 14 days of discontinuing study medication, or as a result of a serious adverse experience that began within 14 days of discontinuing study drug. All deaths occurred in Phase IIb/III Chronic Exposure Studies (OA, RA, AS, CLBP); none occurred in Phase I/Clinical Pharmacology, Acute Analgesia, or Acute Gouty Arthritis studies.

All deaths were adjudicated by the Vascular Events Adjudication Committee to determine specific cause of death.

Table 17 and Figure 28 summarize mortality rates (per 100 patient-years of exposure in each treatment group), including total, CV, thrombotic CV, and non-CV mortality. The rates, calculated by dividing the absolute number of fatalities by the total treatment exposure, are provided to factor in imbalances in exposure between treatment groups. The mortality rates are low and similar across all treatment groups.

The overall mortality rates in the etoricoxib treatment group appear to be resulting approximately equally from nonthrombotic events (e.g., trauma, neoplasm) and thrombotic CV adverse experiences (e.g., acute myocardial infarction, thrombotic CVA, sudden and/or unexplained death). Out of a total of 20 events for etoricoxib, 11 were nonthrombotic. For naproxen, out of a total of 5 events, 2 were thrombotic and 3 were nonthrombotic. For non-naproxen NSAIDs, out of a total of 2 events, both were thrombotic. Based on these data, there is no evidence of significant difference between treatment groups or by category.

Table 17

Summary of Deaths
Chronic Exposure Studies (EDGE Study not Included)

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

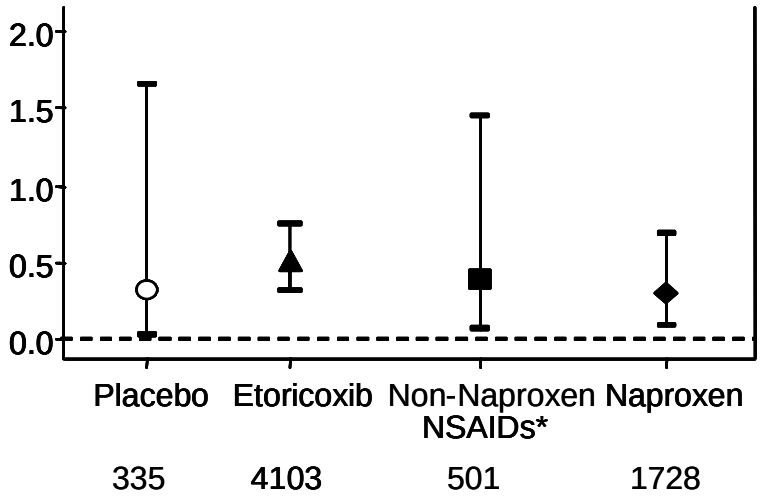
† Total Deaths includes CV Deaths + Non-CV Deaths.

‡ Thrombotic CV Deaths is a subset of CV Deaths, which excludes non-thrombotic CV deaths (SAE of fatal arterial hemorrhage, AN 12201 [etoricoxib 120 mg, Protocol 026] and AN 9348 [SAE of fatal hemorrhagic stroke, 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).

Figure 28

Deaths Rates Per 100 Patient-Years (95% CI)
Chronic Exposure Studies (EDGE Study not Included)



* ibuprofen and diclofenac

Mortality in the EDGE Study

All deaths that occurred in the EDGE study on therapy or within 28 days of the last dose of study therapy were also adjudicated by the Vascular Events Adjudication Committee.

Table 18 summarizes mortality rates (per 100 patient-years of exposure in each treatment group), including total, CV, thrombotic CV, and non-CV mortality. Consistent with the development program data, there is no evidence of any significant difference between treatment groups or by category.

Five additional patients died during the off study drug period (>14 days): 2 in the etoricoxib group, and 3 in the diclofenac group.

Table 18

Summary of Deaths
The EDGE Study

	Etoricoxib PYR=2792	Diclofenac PYR=2608
Counts—Rates per 100 PYR (95% CI) [number of patients]		
Total death†	0.29 (0.12, 0.56) [8]	0.23 (0.08, 0.50) [6]
CV Deaths	0.14 (0.04, 0.37) [4]	0.12 (0.02, 0.34) [3]
Thrombotic CV Deaths‡	0.11 (0.02, 0.31) [3]	0.04 (0.00, 0.21) [1]
Non-CV Deaths	0.14 (0.04, 0.37) [4]	0.12 (0.02, 0.34) [3]

† Total Deaths includes CV Deaths + Non-CV Deaths.
‡ Thrombotic CV Deaths is a subset of CV Deaths.
PYR= Patient-years.
CV=Cardiovascular.

8. Ongoing Studies to Further Assess Thrombotic CV Safety

Description of Studies

In support of an ongoing assessment of the thrombotic CV safety profile of etoricoxib in the patient populations who require therapies with NSAIDs and selective COX-2 inhibitors, 3 individual large, randomized, double-blind, active comparator-controlled clinical studies were designed (Table 19):

1. EDGE: study is complete, with thrombotic cardiovascular data summarized in Section 6.4.2
2. EDGE II: currently ongoing, data not yet available
3. MEDAL: currently ongoing, data not yet available

These studies were designed so that together, as reflected in a prespecified data analysis plan (DAP) and discussed below, they would firmly establish the CV safety profile of etoricoxib relative to the non-selective NSAID diclofenac, thus addressing the clinically relevant comparison of a selective COX-2 inhibitor to an NSAID without potent anti-platelet effects in a patient population requiring treatment.

Table 19

Summary and Description of Ongoing Etoricoxib Studies to Further Assess Thrombotic CV Safety

	EDGE	EDGE II	MEDAL
Primary objective	Compare GI tolerability of etoricoxib to diclofenac in OA patients	Compare GI tolerability of etoricoxib to diclofenac in RA patients	1. compare CV safety of etoricoxib to diclofenac, based on data combined from 3 studies (EDGE, EDGE II, MEDAL) 2. compare CV safety of etoricoxib to diclofenac, based on data from MEDAL
Study size	7111	~4090	~23,450
Patient population	OA	RA	OA (~76%), RA (~24%)
Study therapy	Etoricoxib 90 mg vs. diclofenac 150 mg (1:1)	Etoricoxib 90 mg vs. diclofenac 150 mg (1:1)	Etoricoxib (60 mg in OA, 90 mg in RA) vs. diclofenac 150 mg (1:1)
Duration of therapy [mean (max) in months]	9 (16)	19 (34)†	20 (40)‡
Data available	Study complete	2006	2006

† Duration of EDGE II was defined as 2 years from Last Patient Randomized; since study is ongoing the duration of therapy provided represents a prediction

‡ MEDAL is endpoint driven and will complete when prespecified number of Confirmed Thrombotic CV serious adverse experiences have occurred in both MEDAL alone and from all 3 studies (EDGE, EDGE II, MEDAL) combined; since study is ongoing the duration of therapy provided represents a prediction

Study Objectives

The primary objective of both EDGE and EDGE II is to compare the GI tolerability of etoricoxib to diclofenac. As part of the assessment of general safety and tolerability in these studies, thrombotic CV safety data are collected and adjudicated using the same adjudication process as was employed during the clinical development program. The primary objective of MEDAL is to compare the CV safety of etoricoxib to diclofenac. As such, MEDAL is designed as an endpoint driven CV outcomes study and is sufficiently powered (81%) for a comparative assessment of thrombotic CV safety using data from MEDAL alone.

In order to increase the precision and robustness of the comparison of thrombotic CV safety between etoricoxib and diclofenac, a DAP was written to prespecify a combined analysis of thrombotic CV safety using the data from all three studies (EDGE, EDGE II, MEDAL). The DAP specifies that the primary assessment of thrombotic CV safety will be based on the thrombotic CV safety data from all 3 studies combined. The studies were designed with this objective in mind and thus allow for this combined analysis. The secondary assessment of thrombotic CV safety will be based on the data from MEDAL alone as indicated above.

Patient Populations

These three studies were designed to evaluate an arthritic patient population which requires COX-inhibiting agents, and to do so under conditions that closely emulate clinical practice. Studying these patients ensures that the thrombotic CV safety data from these studies will be directly relevant to the patient population in clinical practice which requires these therapies. Both OA and RA patients where chosen. Of the approximately 34,600 patients enrolled in total across all 3 studies, approximately 10,000 have RA, a particularly important patient population to evaluate given the overall increased risk of thrombotic CV adverse experiences in patients with RA [74] and the fact that these patients can require higher doses of non-selective NSAIDS and selective COX-2 inhibitors and may be treated for longer periods of time.

The majority of the data will come from the MEDAL study. In MEDAL, the OA and RA patients enrolled extend across a range of CV risk. Patients with cardiac risk factors as well as patients with known CV disease are included. As a result, the study includes a significant number of patients on low-dose aspirin (anticipated to be ~35% of all patients).

Etoricoxib Dose

Maximally efficacious doses of etoricoxib are being evaluated in these studies in order to assess the thrombotic CV safety of etoricoxib at the currently recommended doses for chronic use (60 mg in OA, 90 mg in RA). All RA patients in these studies are randomized to either etoricoxib 90 mg or diclofenac 150 mg. The majority, but not all, of the OA patients in these studies are randomized to either etoricoxib 60 mg or diclofenac. The exceptions are: (1) the patients in the EDGE study, who received 90 mg; and (2) approximately 4000 OA patients (out of a total of 17,764, or approximately 23%) in MEDAL, who were randomized to either etoricoxib 90 mg or diclofenac 150 mg. Etoricoxib 90 mg is above the currently recommended dose for OA (60 mg) and thus provides important safety data at a supratherapeutic dose of etoricoxib for OA. In total, these data will support analyses of CV safety by dose.

Comparator Agent

No placebo control is included in these 3 studies because the studies are designed to evaluate patients with arthritis (either OA or RA) sufficiently severe to justify chronic symptomatic therapy over an extended period of time. Inclusion of a placebo treatment arm can be justified only for a short period of time in a patient population requiring symptomatic treatment.

Diclofenac is the active comparator in all 3 of these studies. The rationale for choosing diclofenac is well-founded, and the key reasons are summarized as follows:

- Diclofenac is considered an effective NSAID used extensively worldwide for the management of symptoms associated with both OA and RA. Providing effective therapy is critically important in order to maintain patients in these studies for an extended period of time.
- Diclofenac inhibits both COX-1 and COX-2 at doses recommended for clinical use. However, diclofenac only transiently and reversibly inhibits thromboxane-mediated platelet aggregation. Based on this, diclofenac would not be expected to demonstrate any cardioprotective effect [75; 6]. The outcomes study results therefore, would not be confounded by the potential for aspirin-like antiplatelet effects, as likely would have been the case if naproxen were the NSAID comparator.
- Given the emerging concern about the potential for certain NSAIDs (i.e. ibuprofen) to mitigate the anti-platelet effect of aspirin, it was important to choose an NSAID comparator that did not have this property. Due to ibuprofen's interference with aspirin's ability to inhibit platelet function and the possible clinical manifestations of this pharmacodynamic interaction, use of ibuprofen as a comparator may represent an ethical concern for patients who may be taking low dose aspirin for cardiovascular prophylaxis. Indeed, an elevated rate of CV events in such patients would confound the interpretation of observing similar rate of events compared to etoricoxib, should such have been the result. Diclofenac, on the other hand, has been evaluated for this interaction and has been shown not to interfere with aspirin's antiplatelet effects [75].
- Diclofenac is generally well-tolerated, with a favorable renovascular profile (i.e., hypertension, edema); in fact, renovascular data from the EDGE study demonstrated a difference in blood pressure effects favoring diclofenac when compared with etoricoxib. With the established longer term CV sequelae of elevated blood pressure in mind, a comparison of thrombotic CV safety between etoricoxib and diclofenac can be considered conservative.
- Diclofenac is dosed twice daily which provides an important convenience factor for patients participating in long term clinical trials which also improves compliance as compared to more frequent dosing.

Numerous other NSAIDs were considered for inclusion, but only two were considered plausible; naproxen and ibuprofen. With regard to naproxen, when considering the totality of the randomized clinical trials data, including data for rofecoxib [17], lumiracoxib [8], and now etoricoxib, the weight of evidence continues to support a lowering of CV event rate with naproxen relative to a selective COX-2 inhibitor. In light of this consistent observation, inclusion of naproxen as an active comparator in the current etoricoxib outcomes studies would not be informative to further understanding of the CV safety profile of etoricoxib. With regard to ibuprofen, as discussed above, due to its interference with aspirin's ability to inhibit platelet function, its use as a comparator potentially represented an ethical concern specific to patients taking low dose aspirin for cardioprotection and thus was not chosen.

In order to precisely define the CV risk of etoricoxib, the DAP details an assessment of CV risk in comparison to a single comparator, diclofenac, using the largest database ever established for a selective COX-2 inhibitor or non-selective NSAID with the exception of aspirin, consisting of approximately 34,600 patients. To generate data as precise with an additional comparator agent would require an additional treatment arm equivalent to the size of one treatment arm in MEDAL (i.e. approximately 11,750 patients). A study of this magnitude is not feasible and would likely not be successfully completed. The alternative approach would be to add a second comparator while keeping the overall study size the same. Such a design is not suitable as it would not be adequately powered for a comparison of etoricoxib to either comparator arm alone, resulting in two underpowered point estimates of CV risk.

In consideration of these 2 key design features, namely the number of comparators and the specific choice of comparator, results from such a study design (one with an adequately powered analysis of etoricoxib to diclofenac) should provide an adequate and thorough assessment of the CV safety of etoricoxib in the intended patient population for treatment.

Study Duration

The actual mean duration of study therapy in EDGE was 9 months, with a median duration of 11 months; the maximal duration of study therapy in EDGE was 16 months. The study durations for EDGE II and MEDAL can only be estimated at this time as these studies are currently ongoing. The study duration of EDGE II will be approximately 24 months from the time the last patient is enrolled. The study duration of MEDAL is not specified as it is an endpoint-driven study, designed to complete when the prespecified number of CV endpoint events has accrued. Although the actual average duration of study therapy in EDGE II and MEDAL cannot be ascertained at this time, the mean durations of these studies are estimated to be 19 and 20 months, respectively. Based on current study designs, the estimated duration of exposure for EDGE II is approximately 2000 patient-years after 18 months and approximately 700 patient-years after 2 years; for MEDAL, the estimated duration is greater, with approximately 13,000 patient-years of exposure after 18 months and approximately 7000 patient-years of exposure after 2 years. Combined data from these 3 studies (EDGE, EDGE II, and MEDAL) will provide an extensive amount of long term safety data, with exposure greater than that collected from the rofecoxib APPROVe study (3041 patient-years for rofecoxib and 3315 patient-years for placebo).

External Data Safety Monitoring Board (ESMB)

The study is monitored by an ESMB, which was chartered when MEDAL was initiated. Membership includes representation with relevant experience in clinical practice, biostatistics, and clinical trials conduct. The ESMB performs bimonthly data review and meets face-to-face at least twice yearly. At the most recent meeting in Nov-2004, the ESMB recommended to continue MEDAL and EDGE II without modification based upon data that included more than 300 Confirmed Thrombotic CV serious adverse experiences and included more than 3000 patient who were on therapy for greater than 18 months. The ESMB will continue to meet at least twice a yearly as mandated by the charter.

Summary

MEDAL and its prespecified primary analysis of Confirmed Thrombotic CV serious adverse experiences from MEDAL, EDGE and EDGE II combined will generate adequate and sufficient data for a regulatory assessment of etoricoxib's CV safety profile. It is the largest NSAID trial ever designed and includes an appropriate active comparator (diclofenac) for purposes of comparative CV safety. MEDAL is generating safety data in the patient population intended for treatment, and includes patients with a range of CV risk and both aspirin users and nonusers. It will provide information to assess effect of dose (etoricoxib 60 mg and 90 mg included) and disease (OA versus RA). Perhaps most importantly in consideration of the results of the rofecoxib APPROVe study, MEDAL will provide an extensive amount of long term safety data.

9. Overall Conclusions

- The data as summarized above have resulted in etoricoxib's approval worldwide in 60 countries and are under review by the FDA.
- Etoricoxib has demonstrated efficacy in the treatment of OA, RA, AS, CBLP, acute gouty arthritis, and acute pain including primary dysmenorrhea; and has demonstrated anti-inflammatory properties that are comparable and in some cases, superior to nonselective NSAIDs.
- Etoricoxib has a substantially improved GI safety profile compared with nonselective NSAIDs. In 2 large endoscopy studies, etoricoxib 120 mg is associated with an incidence of endoscopic ulcers significantly lower than ibuprofen and naproxen, but greater than placebo. Analysis of all upper GI clinical events demonstrates that etoricoxib use is associated with a consistently lower incidence of upper GI clinical events than nonselective NSAIDs, with the results driven by comparisons to naproxen.
- The GI tolerability profile of etoricoxib is superior to that of nonselective NSAIDs, as evidenced by significantly lower new use of gastroprotective agents and significantly fewer discontinuations due to digestive system adverse experiences with etoricoxib than with nonselective NSAIDs. Superior GI tolerability was also established versus diclofenac in the EDGE study.
- Etoricoxib, at doses recommended for chronic use (60 mg and 90 mg) and extending up to the dose recommended for acute pain and acute gouty arthritis (120 mg), manifests effects on blood pressure that are greater than those of placebo but generally similar to those of NSAIDs.
- The incidence of edema-related adverse experiences with etoricoxib is low and generally of minimal consequence during chronic use at doses up to 120 mg daily and remains low after more than 1 year of therapy. The effects of etoricoxib on edema and body weight are generally similar to comparator NSAIDs.
- Data on thrombotic CV serious adverse experiences in the etoricoxib development program are limited by the duration of the placebo-controlled data (up to 12 weeks in duration) and the quantity of the long-term active comparator-controlled data. In analyses of thrombotic CV serious adverse experiences, including data from the EDGE study, there is no evidence of a discernible difference in event rates among patients taking etoricoxib, placebo, or non-naproxen NSAIDs. Naproxen 500 mg twice daily, however, is associated with a lower incidence of thrombotic CV serious adverse experiences than etoricoxib. The difference begins shortly after initiation of therapy.

- Revised labeling, which already includes a precaution for patients with a medical history of ischemic heart disease, has been distributed to countries in which etoricoxib is marketed and now includes information on the CV safety results from the etoricoxib EDGE study, results from the rofecoxib APPROVe study, and results of the parecoxib/valdecoxib study in patients following coronary artery bypass grafting. A recommendation against the use of etoricoxib by patients who have recently undergone coronary artery bypass graft surgery or angioplasty or in patients with acute coronary syndrome is also included.
- Appropriately designed studies are currently ongoing to further assess the CV safety of etoricoxib in patients who require treatment with NSAIDs or selective COX-2 inhibitors.

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