

FDA Presentation: Analysis of Cardiovascular Thromboembolic Events with Etoricoxib: Joel Schiffenbauer MD

JOINT MEETING OF THE ARTHRITIS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

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Highlights

CV ENDPOINTS:

- **COMPOSITE VS. INDIVIDUAL COMPONENTS OF ENDPOINT:** Merck proposed a composite cardiovascular endpoint but FDA also looked at the components of the composite endpoint.
- **CONFIRMED EVENTS:** FDA will present data for “confirmed thrombotic cardiovascular serious adverse events” 1) for the entire NDA excluding the EDGE study, and 2) for the EDGE study alone.

NON-EDGE DATA:

- **RISK RATIOS FOR NON-EDGE DATA:** “Across the NDA” (exclusive of the large EDGE study) the risk ratios, based on small numbers of events, were calculated:
 - **VS. PLACEBO:** Etoricoxib 1.25 (7 patients) versus 1.19 for placebo (4 patients).
 - **VS. NON-NAPROXEN NSAIDS:** Etoricoxib 0.79 versus non-naproxen comparators 0.80 (all on diclofenac).
- The Kaplan-Meier graph showed a shorter time-to-event for the etoricoxib group.
- **VS. NAPROXEN:** Etoricoxib 1.37 versus naproxen 0.81. The Kaplan-Meier analysis “shows a separation of the two curves almost throughout the entire exposure.”

EDGE TRIAL:

- **NON-INFERIORITY DEFINED AS <1.3 HAZARD RATIO:** For the 7,100-patient EDGE study in osteoarthritis, the “sponsor defined a non-inferiority margin to diclofenac for cardiovascular events as the upper limit of the 95 percent confidence interval for the hazard ratio of 1.3”.
- **30% ON ASPIRIN:** Aspirin was used in 30% of patients which might have reduced cardiovascular risk in a COX-2 setting.
- **PREVIOUS COX-2 USE ALLOWED:** “previous COX-2 use was allowed and this could potentially lead to depletion of susceptible individuals to a cardiovascular event.”
- **K-M CURVES CONVERGE AT 12 MONTHS:** In the Kaplan-Meier analysis of CV event rates, “the two groups separate slightly, but the two curves do finally converge at approximately 12 months”.
- **CV RISK SAME IN ASPIRIN USERS BUT SOMEWHAT HIGHER IN NON-ASPIRIN SUBSET:** CV event rates were comparable in aspirin users (12 versus 9 total, and 7 versus 5 cardiac). However, in non-aspirin users there were 15 cardiac events on etoricoxib versus 10 on diclofenac, and 12 MIs versus 6 on diclofenac.
- **MORE HYPERTENSION ON ETORICOXIB:** Hypertension-related risk was higher with etoricoxib: 5 versus 2 for hypertension-related SAE, and 69 versus 30 for “hypertension-related AE associated with systolic blood pressure greater than 180, or diastolic greater than 110”. Similarly, a graph over 12-months therapy of the “cumulative incidence of new use of anti-hypertensive medications” showed that “the two curves separate almost throughout the entire 12-month period.”
- **MORE HEART FAILURE ON ETORICOXIB:** There was also an increase in “congestive heart failure-related adverse events”, 14 versus 6.

MORTALITY DATA:

- **PLACEBO = NAPROXEN < NON-NAPROXEN NSAIDs < ETORICOXIB:** Looking at mortality data across the NDA, “the placebo group is similar to naproxen, followed by the non-naproxen non-steroidals, and then etoricoxib”.

CONCLUSIONS:

- **TREND TO INCREASE IN CV EVENTS:** In the NDA “etoricoxib trends worse in terms of cardiovascular thromboembolic events, particularly cardiac and MI. The one common thread throughout all the comparators does appear to be the cardiac system.”
- **ETORICOXIB & ROFECOXIB SHOW SAME INCREASE IN CV EVENTS VS. NAPROXEN:** “Comparisons of etoricoxib to naproxen for the cardiovascular events is similar to what you have seen for rofecoxib and the naproxen comparisons.”
- **UNFAVORABLE TRENDS IN NON-ASPIRIN USERS IN EDGE TRIAL:** “There are trends in the EDGE study for cardiac events, worse for etoricoxib, and that is seen mainly in the non-aspirin users.”

Presentation Text

Thank you and good morning. My name is Joel Schiffenbauer. I am going to be presenting an analysis of cardiovascular thromboembolic events with etoricoxib.

I will be presenting the results of trials for the following indications listed here in the NDA. In addition, I will be presenting results of the EDGE trial separately from those of the trials here.

I will first present briefly exposure data followed by mortality data and then spend the remainder of the time discussing the cardiovascular thromboembolic events data. Again, I will present data first for the NDA and separately for the EDGE study.

First, exposure. This slide summarizes the chronic exposure to etoricoxib across the NDA. As you can see for the 60, 90, and 120 mg doses, which were the proposed doses for the drug, the total number of patients is shown here and the mean number of days is shown here.

For the EDGE study, there was approximately 3,500 patients in each arm, exposed for a mean of 9 months. Total patient years is shown at the bottom.

Let me turn now to the mortality data. This is the mortality data across the NDA. Rates are shown as per 100 patient years, and I have listed the comparators here, placebo, non-naproxen non-steroidals, and naproxen.

If we first look at the first line of total deaths, we can see that the rate of deaths in the placebo group is similar to naproxen, followed by the non-naproxen non-steroidals, and then etoricoxib.

Let me next draw your attention to the third line, thrombotic cardiovascular deaths. There were no deaths in the placebo group, followed by naproxen, etoricoxib, and then non-naproxen non-steroidals.

These 2 events I would point out occurred at greater than 36 months exposure to the non-naproxen non-steroidals, and I will come back to this point when I present the Kaplan-Meier analysis looking at non-naproxen non-steroidals.

The deaths in the EDGE study, the total deaths are similar, 8 and 6, for cardiovascular thrombotic related, it was 3 and 1.

Let me now move on to a discussion of the cardiovascular thromboembolic events.

The sponsor proposed a composite endpoint, which you have already heard about, which included events related to the cardiac, peripheral, and cerebrovascular system. I will present results for both the composite, as well as the components of the composite, and I think this is an important point because we do not yet know the effects of COX-2 inhibitors on each of these specific cardiovascular events.

In addition, I will not present data for APTC events or investigator-reported events. Although the numbers vary slightly, the trends are always in the same direction as the events that I will show here.

These events were referred to an Adjudication Committee, that you have heard about already, and after being reviewed in that committee, were then described as confirmed cardiovascular thromboembolic events.

This slide shows an analysis of the confirmed thrombotic cardiovascular serious adverse events across the NDA.

This is exclusive of the EDGE study. The sponsor performed 3 comparisons - etoricoxib to placebo, etoricoxib to non-naproxen non-steroidals, and etoricoxib to naproxen.

The number of patients, the cases in patient years of exposure is shown here, rates, and relative risk. I will show this slide over again.

First, let me start on the first line. I draw your attention to the rate of events in the etoricoxib group 1.25 versus placebo 1.19 for the relative risk shown here, and an analysis of those events is shown in this slide.

These are the rates I showed you, 1.25 and 1.19. There were a total of 7 patients in the etoricoxib group versus 4 in placebo, and this breaks down to 4 cardiac events, which are listed here - MI, fatal MI, unstable angina, and sudden death versus zero in placebo.

The number of events in peripheral and cerebrovascular is similar although the rates do vary slightly.

Let me point out here that in some of these slides, these numbers will not necessarily add up. That is for two reasons. One is an individual patient may have more than one event, and they would therefore be listed in more than one category, and, secondly, for the sake of clarity and brevity, I left out in some instances all the events.

This is the Kaplan-Meier estimate of time to event for the placebo comparison. Note that this is only 3 months in duration. There are very little differences between the two groups.

Let me move on then to the etoricoxib/non-naproxen comparisons. Here is the rate, 0.79 and 0.80, and I will show you that in next slide. Here are the rates again, 0.79 and 0.80. These are composed of 12 patients in the etoricoxib group versus 4 in the combined, and by that I mean combined exposure to diclofenac and ibuprofen. You can see, however, exposure to ibuprofen is rather small and there were no events, so all of the events come from the diclofenac exposure.

If we examine the breakdown of these 12 events, you can see there were 11 cardiac events in the etoricoxib group for the rate shown here versus 2 in the combined for this rate, and that is further broken down to 3 MIs versus zero, 2 and 1 of fatal MIs, and then the rest you can see here. There are 2 and 2 events in the cerebrovascular system.

You have seen this previously, but let me make several points about this Kaplan-Meier analysis for the non-naproxen and nonsteroidal comparisons. First of all, you will note that the length of exposure is out to 36 months when there are relatively few patients still present in the studies.

Secondly, there were 4 events in the non-naproxen non-steroidals, which is shown by the solid line. Three of those events occurred at greater than 36 months exposure. Two of those 3 events were the deaths that I described in the earlier slide.

In contrast, there were 12 events in the etoricoxib group, 11 out of those 12 events occurred at approximately 26 months or earlier. So, there is a difference in the time to event as

demonstrated by this Kaplan-Meier analysis.

Lastly, let me turn to the etoricoxib/naproxen exposure. Here are the rates, 1.37 and 0.81. Again, here are the rates, 1.37 and 0.81. There were 34 patients in etoricoxib versus 14 in naproxen, and that is broken down into 21 cardiac versus 9 for the rate shown here, 10 MIs versus 5, and you can see the remainder.

For peripheral, there was a slight imbalance, 5 events in naproxen versus 2 in peripheral, however, when we come back to the cerebrovascular system, there were 12 versus 2, which included 10 ischemic strokes versus zero. Again, you have seen the Kaplan-Meier analysis, which shows a separation of the two curves almost throughout the entire exposure.

Let me turn now to the analysis of cardiovascular events in the EDGE study, and start by making a few points. There were 7,100 patients. It was designed as a GI tolerability study in which cardiovascular data was collected.

The sponsor defined a non-inferiority margin to diclofenac for cardiovascular events as the upper limit of the 95 percent confidence interval for the hazard ratio of 1.3.

In addition, there were several concerns that I would like to emphasize. First, it was designed as a non-inferiority trial, there was no placebo. Diclofenac was the only comparator, and as we have heard here, and there is data in the literature to support the relative COX-2 selectivity of diclofenac.

Next, there was only osteoarthritis patients studied. There were no rheumatoid arthritis patients in this study. We know that rheumatoid arthritis itself confers cardiovascular risk.

The next two bullets relate to maneuvers that could potentially, in the context of a non-inferiority trial, make it difficult to identify differences between the two treatment groups.

So, for example, there was 30 percent aspirin use. If we believe that aspirin is cardio-protective even in the context of COX-2 inhibitor, this could make it difficult to discern any differences between the two groups.

In addition, previous COX-2 use was allowed, and I have listed here what that was, and this could potentially lead to depletion of susceptible individuals to a cardiovascular event.

Lastly, although it is important to study high-risk patients, if these high-risk patients are on aspirin, that may be a problem in differentiating the two groups. In addition, if there are more events in these high-risk patients, it could increase the background events, and again in the context of a non-inferiority trial, may make it difficult to differentiate the two treatment groups.

So, you have seen this Kaplan-Meier analysis. Again, the two groups separate slightly, but the two curves do finally converge at approximately 12 months.

This is a breakdown of the events in the EDGE trial. There were 35 patients in the etoricoxib group versus 30 in diclofenac for the rates given here. If we look at a further breakdown of the

components, we see there were 27 cardiac-related events versus 19 for the rates given here. For MI, there was 19 versus 11. For cerebrovascular events, there was 7 and 7 with a slight imbalance in ischemic strokes of 6 in diclofenac versus 3 in etoricoxib.

I think it is important, I mentioned earlier that aspirin use may be a problem. I broke down the number of events by aspirin and non-aspirin users, and I have just provided the number of events, the patient years of exposure are fairly similar.

You can see that by aspirin users, there is little differences between the groups, 12 versus 9 here for cardiac events, 7 and 5. However, when you look at the non-aspirin users, the differences are more pronounced. There were 15 cardiac events in etoricoxib versus 10 in diclofenac, and 12 MIs versus 6.

There was some concern about hypertension. Some issues were raised about that yesterday. I show some data for hypertension-related adverse events in the EDGE trial. These types of adverse events could include anything from a hypertensive crisis, malignant hypertension to systolic blood pressure increase among other events.

This is an analysis of patients with serious hypertension-related adverse events. There were 5 in etoricoxib versus 2 in diclofenac, and then another category, hypertension-related AE associated with systolic blood pressure greater than 180, or diastolic greater than 110, and there were 69 cases here versus 30 in diclofenac.

Then, this is a cumulative incidence of new use of anti-hypertensive medications. The upper line is etoricoxib, the lower line is diclofenac. You can see that the two curves separate almost throughout the entire 12-month period.

Lastly, a description of congestive heart failure-related adverse events. This is the incidence of CHF pulmonary edema-related or cardiac failure adverse events. There were 14 versus 6.

In summary, in the NDA, etoricoxib trends worse in terms of cardiovascular thromboembolic events, particularly cardiac and MI. The one common thread throughout all the comparators does appear to be the cardiac system.

There are differences in the cerebrovascular or peripheral system,

but those are inconsistent depending on the comparator.

Comparisons of etoricoxib to naproxen for the cardiovascular events is similar to what you have seen for rofecoxib and the naproxen comparisons.

I have outlined some trial design concerns in the EDGE study, which I presented, and as you have already heard, there are two ongoing trials of similar design, which I believe have similar concerns.

There are trends in the EDGE study for cardiac events, worse for etoricoxib, and that is seen mainly in the non-aspirin users.

Thank you.

Presentation Slides

Note: Some of the slides presented may not be included below.



Etoricoxib

- NDA indications include: OA, CLBP, RA, AS, acute gout, acute pain, dysmenorrhea
 - Proposed doses: 60 and 90 mg chronically and 120 mg acutely
- EDGE study: Etoricoxib vs. Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness

Etoricoxib

- Exposure
- Mortality data
- CV/TE data
 - NDA
 - EDGE

Etoricoxib Exposure

Chronic Exposure to Etoricoxib Across the NDA

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

EDGE Study

	Etoricoxib 60 mg (N=3092)	Diclofenac 150 mg (N=3518)	Total (N=7111)
Duration of study therapy (months)			
Mean	8.7	8.9	9.1
SD	4.4	4.5	4.5
Median	11.5	11.3	11.4
Range	0.5 to 16.5	0.5 to 16.6	0.5 to 16.6
Total patient years	2799	2684	

Etoricoxib Mortality Data

NDA/Deaths (rates are per 100 PYR)

	Placebo PYR=366	Etoricoxib PYR=4129	Non-exposure PYR=527	Supernov PYR=1728
Total deaths	1 (rate 0.28)	29 (0.08)	2 (0.38)	1 (0.29)
CV Deaths	0	19 (0.24)	1 (0.38)	1 (0.17)
Thrombotic CV Deaths	0	9 (0.22)	2 (0.38)	1 (0.12)
New CV Deaths	1 (0.28)	19 (0.24)	0	2 (0.12)

EDGE/Deaths

	ETORICOXIB (2792 pt-yrs)	DICLOFENAC (2608 pt yrs)
TOTAL	8	6
CV THROMBOTIC	3	1
CVA (hemorrhagic)	1	2
NEOPLASM	2	3
Other (melanocarcinoma, hemorrhagic shock)	2	0

Etoricoxib CV/TE Events in NDA

Serious Adverse Events Included in Thrombotic CV SAEs

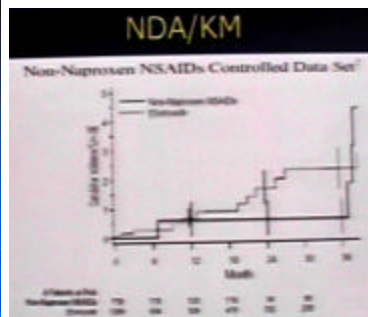
- Cardiac**
 - Acute MI
 - MI/MI
 - Unstable angina
 - Sudden death
- Peripheral**
 - Pulmonary embolism
 - Deep PE
 - Peripher arterial or venous thrombosis
- Cerebrovascular**
 - Ischemic cerebrovascular stroke
 - Fatal stroke
 - TIA

NDA/Absolute Rate & Relative Risk

Comparisons	N	Cases/PYR	Rate	Relative risk (95% CI)
Controlled (thrombotic CV serious adverse events)				
Etoricoxib	2818	7/360	1.25	1.11
Placebo	1767	4/325	1.19	(0.57, 1.81)
Etoricoxib	1266	12/1522	0.79	0.83
Non-exposure NSAIDs	718	4/501	0.80	(0.26, 2.64)
Etoricoxib	1960	34/3480	1.37	1.70
Supernov	1497	14/1727	0.81	(0.41, 1.19)

NDA/Placebo

Endpoint terms	Etoricoxib PIR=560		Placebo PIR=125	
	N	Rate (per 100 PYR)	N	Rate
	Patients with one or more thrombotic CV SAEs	7	1.25	4
Cardiac (MI, Total MI, unstable angina, sudden death)	4	0.71	0	0
Peripheral	1	0.18	2	0.60
Cerebrovascular (ischemic stroke)	2	0.54	2	0.60

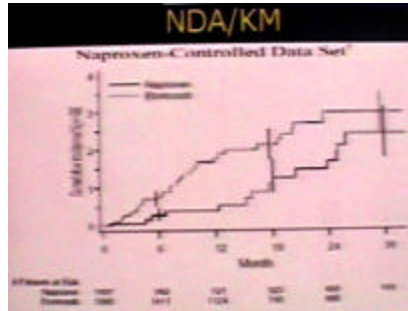


NDA/Absolute Rate & Relative Risk

Comparisons	N	Cases/PYR	Rate	Relative risk (95% CI)
Confirmed thrombotic CV versus adverse events				
Etoricoxib	2818	7/560	1.25	1.11
Placebo	1767	4/335	1.19	(0.32, 3.81)
Etoricoxib	1266	12/1522	0.79	0.83
Non-naproxen NSAIDs	728	4/501	0.80	(0.26, 2.64)
Etoricoxib	1960	14/2480	2.37	2.08
Naproxen	1917	14/2221	2.42	(0.25, 2.58)

NDA/Naproxen

Endpoint	Etoricoxib PIR=2490		Naproxen PIR=1727	
	N	Rate	N	Rate
Patients with one or more thrombotic CV SAE	24	1.37	14	1.80
Cardiac	21	0.85	9	0.52
MI	10	0.40	5	0.29
Fatal MI	2	0.08	1	0.07
Sudden Death	1	0.12	0	0
Unstable Angina	6	0.24	3	0.17
Peripheral	2	0.08	5	0.29
Cerebrovascular	12	0.49	2	0.12
Ischemic Stroke	10	0.40	0	0
Fatal Ischemic Stroke	0	0	1	0.06



Etoricoxib

CV Events in EDGE Study

Summary

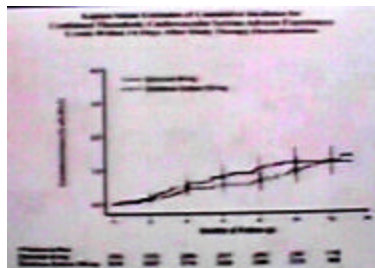
- In NDA, etoricoxib trends worse in terms of CV/TE particularly cardiac/MI
- Comparisons of etoricoxib to naproxen for CV/TE events are similar to rofecoxib/naproxen comparisons
- Trial design concerns in EDGE (2 ongoing trials of similar design)
- Trends in EDGE for cardiac events worse for etoricoxib, mainly in non-ASA users

EDGE

- 7000 patient GI tolerability study; collect CV data; non-inferiority to diclofenac (upper limit of 95% CI for hazard ratio is 1.3)

Issues:

- Non-inferiority trial (no placebo)
- diclofenac only comparator
- only OA, no RA
- ASA use (30%)
- previous Cox-2 use allowed (15% rofecoxib; 13% celecoxib; 5% valdecoxib)
- 2500 with >2 CV risk factors



EDGE/Confirmed Thrombotic CV SAEs

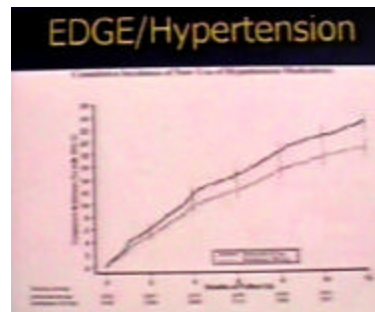
Endpoint	Etoricoxib PIR=2789		Diclofenac PIR=2507	
	N	Rate	N	Rate
Patients with one or more thrombotic CV SAE	35	1.25	38	1.35
Cardiac	27	0.93	19	0.73
MI	19	0.65	11	0.42
Sudden Death	2	0.07	1	0.04
Unstable Angina	6	0.22	7	0.27
Peripheral	3	0.11	4	0.15
Cerebrovascular	7	0.25	7	0.27
Ischemic Stroke	5	0.18	6	0.23
Fatal Ischemic Stroke	1	0.04	0	0

EDGE/ASA Users Combined

	Etoricoxib		Diclofenac	
	Number of Events	Number of Events	Number of Events	Number of Events
Cardiac	12	9		
MI	7	5		
MI plus unstable angina	11	9		
CNS	4	3		
PVS	1	1		
Cardiac plus CNS	16	12		

EDGE/Hypertension

	Etoricoxib 90 mg N=3593		Diclofenac 150 mg N=3518	
	n	%	n	%
Hypertension				
Number (%) of patients with serious hypertension related AE	5	(0.14)	2	(0.05)
With a hypertension related AE associated with systolic >180 mm Hg or diastolic >110 mm Hg	49	(1.9)	30	(0.9)



EDGE/CHF

Adverse Experience	Etoricoxib N (%)	Diclofenac N (%)
Incidence of CHF, pulmonary edema-related, or cardiac failure	14 (0.4)	6 (0.2)
Cardiac failure	1 (0)	0 (0)
Cardiac failure congestive	12 (0.3)	6 (0.2)