Trends-in-Medicine

November 2004

By Lynne Peterson

Quick Pulse

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

The Cardiovascular Safety of Cox-2 Inhibitors

With Merck's Vioxx (rofecoxib) now off the market, how safe are the other Cox-2 inhibitors on the market – Pfizer's Celebrex (celecoxib) and Bextra (valdecoxib)? What do the cardiovascular problems with Vioxx mean for other Cox-2 inhibitors in development, including Merck's Arcoxia (etoricoxib) and Novartis's Prexige (lumiracoxib)? There is no easy or quick answer, and this issue may haunt these products for some time.

On September 30, 2004, Merck announced that it was withdrawing its cyclooxygenase-2 (Cox-2) inhibitor Vioxx from the market because of the risk of serious cardiovascular events – strokes and heart attacks. The decision was due to a safety analysis of a long-term, ongoing, trial to see if Vioxx could prevent the recurrence of colon polyps. The data safety monitoring board for the three-year, prospective, randomized, double-blind, 2,600-patient APPROVe trial found twice the risk of a CV event with Vioxx than with placebo and recommended the trial be halted.

Merck chose to "take the high road" and withdraw Vioxx rather than face stricter labeling. Raymond Gilmartin, Chairman, President, and CEO of Merck, said, "We are taking this action because we feel it is in the best interests of patients. It could have been possible to market Vioxx with new labeling, but given alternative therapy and the questions raised, we think voluntary withdrawal is the best route."

In the first 13 months of APPROVe, there was no increased risk of CV events between Vioxx and control. However, the study also found that beginning at 18 months there was a discernible and unexplained risk of CV events in Vioxx patients.

More than two million people world-wide were taking Vioxx at the time of the withdrawal, and Merck's announcement caught doctors and patients off-guard. It also caught the attention of Congress, and legislators, including Senate Finance Committee Chairman Sen. Charles Grassley (R-Iowa), demanded a detailed explanation.

Vioxx was not the first Cox-2 inhibitor to get FDA approval. Pfizer's Celebrex was approved by the FDA on December 31, 1998, and Vioxx was not approved until May 13, 1999.

Yet, the cardiovascular safety of Vioxx had been in question ever since the release of the results of the VIGOR trial in June 2000. VIGOR reported an increased risk of serious CV events in patients taking Vioxx compared to naproxen (an NSAID). In February 2001, the FDA's Arthritis Advisory Committee met to discuss the implications of the VIGOR findings, and the Agency later issued Vioxx label changes describing an increased risk of CV events with the drug.

At the American College of Cardiology meeting in March 2004, the waters got muddier. A New England insurance carrier's database of ~3 million patients was evaluated retrospectively to determine incidence of cardiovascular events (AMI, stroke) in normotensive and hypertensive arthritis patients from January 1, 1999, through June 30, 2001. This study, funded by Pfizer, found no increased risk with Vioxx in normotensives, but a significantly higher hazard ratio for stroke or AMI in hypertensives with Vioxx compared to Celebrex (p=0.004). An investigator said, "We believe this issue is inherent in the molecules themselves and is not related to the mechanism by which they provide suppression of inflammation."

Even post-withdrawal, Vioxx remains a major topic of interest for physicians, and the CV problems with Vioxx raise questions about the future of other Cox-2 inhibitors – those already on the market as well as ones in development.

At the American College of Rheumatology (ACR) meeting in San Antonio in October 2004, it became clear there is likely to be a long and tough road ahead before new, second-generation Cox-2 inhibitors gain FDA approval. It also looked especially bad for Novartis's Prexige because it (1) already has shown a CV signal, and (2) it is the most selective of all the Cox-2s.

At the press conference announcing the withdrawal of Vioxx, a Merck official tried to distinguish between Vioxx and other Cox-2s, saying, "The result of clinical studies with one molecule do not necessarily apply to others in that class. The clinical significance of the APPROVe trial for long-term use of other drugs in this class – which includes NSAIDs and Cox-2s – is unknown…We, of course, will provide this (APPROVe) data to the regulatory agencies, including the FDA, so they can decide what additional prescribing information or changes are necessary for these other drugs… We will work with regulatory authorities in the 42 countries where Arcoxia is approved to see if changes in prescribing information for this class – including Arcoxia – are warranted. Meanwhile, we will continue our (Arcoxia) development process in the U.S."

FDA officials have said little in public about the Cox-2s in development, though one official said they are providing guidance privately to sponsors. The FDA will hold a public advisory committee meeting in early 2005 that is intended to lead to new guidelines for Cox-2s, but those guidelines are likely to take a fair amount of time to finish. In the meantime, the FDA will be "carefully scrutinizing" new agents, and it appears highly likely that there will be long delays in approval of other Cox-2s – especially if there is any signal of an excess of CV events with a particular agent.

A month after the Vioxx withdrawal – on October 29, 2004 – the FDA issued an "approvable" letter for Arcoxia, asking Merck for additional safety and efficacy data. Arcoxia already is approved and marketed in at least 42 other countries.

NSAIDs and Cox-2 Selectivity

Cox-1 Selectivity *(least down to most)*	Cox-2 Selectivity *(most down to least)*
	Novartis's Prexige (lumiracoxib)
	Merck's Vioxx (rofecoxib)
	Merck's Arcoxia (etoricoxib)
	Pfizer's Bextra (valdecoxib)
	Etodolac
	Boehringer Ingelheim's Mobic (meloxicam)
	Pfizer's Celebrex (celecoxib)
Diclofenac	
Ranbaxy's Nalfon (fenoprofen)	
Ibuprofen	
Naproxen	
Aspirin	
Merck's Indocin (indomethacin)	
Pfizer's Ansaid (flurbiprofen)	
Ketorolac	

The APPROVe Trial

The first scientific presentation of the APPROVe trial results on which Merck made the decision to withdraw Vioxx (rofecoxib) from the market was made at the American College of Rheumatology meeting in San Antonio in October 2004. First, a Merck official reviewed the history of cardiac safety of Vioxx, concluding that prior to APPROVe, the risk of cardiovascular (CV) events in randomized trials was:

- Higher compared with naproxen
- Similar to non-naproxen NSAIDs
- Similar to placebo – but there was limited data beyond two years

Cardiovascular Safety of Vioxx in Osteoarthritis

Trial	CV event rate per 100 patient years			Relative risk
	Vioxx	Non-naproxen NSAIDs	Naproxen	
OA Studies	2.05	1.89	---	1.09
VIGOR	1.67	---	0.7	2.3

Dr. Robert Bresalier, a gastroenterologist with MD Anderson Cancer Center and a member of the APPROVe steering committee presented the findings of APPROVe, a multicenter (107 centers in 30 countries), randomized, placebo-controlled, double-blind trial to determine the effect of three years of 25 mg Vioxx on the recurrence of colon polyps. The CV assessment was pre-specified. As of August 16, 2004, there were 118 investigator-reported CV events in APPROVe – 70 thrombotic events and 49 APTC events. The curves separated between Vioxx and placebo at 18 months, with – interestingly – the placebo curve flattening out at that point but the Vioxx curve continuing to rise. No difference was found by subgroup analysis – not by hypertension, hyperlipidemia, age,

diabetes, aspirin use, etc. Small increases in blood pressure were seen, but Dr. Bresalier said a preliminary analysis found no link, "The mechanism for the difference between the groups remains uncertain, but analyses are ongoing and the patients will be followed for one year after the protocol." A Merck official added, "We did analyses on patients with hypertensive adverse events to see if they were the same ones with CV events...and they were not…The effect size we saw is much larger than you would have expected from the magnitude of the changes in blood pressure." An FDA official also called the placebo flattening "interesting."

Preliminary CV Data from APPROVe Trial

CV events	Event rate per 100 patient years		Relative risk
	Vioxx	Placebo	
Confirmed CV events	45	25	---
Thrombotic	.75	1.48	1.96 (p=.007)
APTC	.48	1.08	2.25 (p=.008)

Merck officials offered these comments on the APPROVe data and Vioxx:

- "Clearly, the FDA needs more public input…and the indications for the class remain unclear."
- On whether patients are still at risk after stopping Vioxx: "There is no data on that…APPROVe has a one year off-treatment period, and we are continuing to follow that…That will be a limited data set, but hopefully it will answer that question."
- "The relative risk was similar in both high and low (CV) risk patients."
- On whether Vioxx is ever likely to come back on the market for a subset of patients or a more narrow indication: "At this point, there is no intention to do that."

The impact of the Vioxx withdrawal

Is the CV problem with Vioxx a class effect?

A Cox-2 expert said, "One has to be very careful on what one means by class – and consider what a Cox-2 selective agent is …It is probably true that sustained Cox-2 inhibition may dispose to thrombosis…but the differences among the Cox-2 inhibitors must also be considered – the effects on blood pressure and PK/PD differences…Cumulative data indicate that patients treated with rofecoxib have increased risk for hypertension, CHF, and CV thrombotic events compared to other NSAIDs…Comparably robust data also indicate that celecoxib does not share these properties…(But) there is insufficient population-based data to determine whether the other Cox-2 selective agents confer an increased CV risk."

Are there any mechanistic explanations that differentiate the Cox-2 inhibitors?

Merck officials could not cite any compelling or mechanistic differences between Vioxx and Arcoxia (etoricoxib) that would suggest Arcoxia is safer, but Novartis researchers offered several reasons that Prexige (lumiracoxib) may be safer than Vioxx – despite an early signal among CABG patients.

Do Cox-2 selective agents have a different CV risk profile than traditional NSAIDs?

An FDA official said, "At this point, there is no definitive evidence. The agents differ in degree of selectivity, and dose response may be an important factor. Traditional NSAIDs may differ in CV toxicity profiles – everyone should remember this." Another expert said there are signals with other NSAIDs, citing these two examples: "If ibuprofen is given before aspirin, it may limit the cardioprotective effects of aspirin…(And) there is a higher risk of admission for CHF in Vioxx and non-selective NSAIDs but not with Celebrex."

PFIZER'S Celebrex (celecoxib)

In early November 2004, the National Post in Toronto, citing Health Canada (the Canadian equivalent to the FDA) documents, reported that Celebrex may have contributed to at least 14 deaths in Canada. The newspaper claimed that reports had been filed showing more than 100 cases of complications associated with Celebrex, including heart attacks, cardiac arrest, heart failure, and stroke. However, Canadian officials apparently still believe the data are inconclusive as to whether there is an increased risk with Celebrex. Health Canada reportedly is reviewing the safety of all Cox-2 inhibitors.

MERCK'S Arcoxia (etoricoxib)

The FDA's request for additional information on Arcoxia before approving it was not surprising since Merck officials and researchers have been unable to offer any explicit ways in which Arcoxia is different from Vioxx that might suggest why Arcoxia shouldn't have the same cardiovascular (CV) risk as Vioxx. An FDA official said, "We know it raises blood pressure and increases salt retention, but there isn't extensive long-term data. We will have to take a close look at it."

The question of an elevated CV risk with Vioxx first arose with the results of the VIGOR trial, and Arcoxia appears to show the same early signal. However, Merck officials denied that VIGOR contained a "missed" signal – and they insisted there isn't any CV risk signal with Arcoxia. A Merck official said, "You need to take into account the time course…People are confusing what you see with naproxen, and what is seen in APPROVe…With Vioxx, lumiracoxib, etc., you see differences vs. naproxen early – in the first year… It is unclear if (the CV risk) is a class effect or an effect that might extend to other NSAIDs as well…What we saw in APPROVe is very

different from what we saw in VIGOR. Over 10 months (in VIGOR), we saw an early separation of curves, with rates lower with naproxen than Vioxx…Over that same treatment period, there is no difference between Vioxx and placebo or non-naproxen NSAIDs (especially diclofenac)…So, it is difficult to view VIGOR as a signal. Given what we've seen with Arcoxia and lumiracoxib – where all seem similar over a year, and the only outlier is naproxen, you have to wonder what is different about naproxen."

On the negative side:

- **Half-life.** The half-life of Arcoxia is longer than for Vioxx (22 hours vs. 17 hours).
- **Selectivity.** Arcoxia's Cox-2 selectivity is similar to Vioxx. One expert described it as slightly less selective than Vioxx, but a Merck official disagreed, saying, "The selectivity of Cox-2s depends on the assay used…By the assay we use Arcoxia is 100, Bextra 30-35, and Vioxx 7-8…And the clinical significance of selectivity, in my opinion, is not determined…I believe Arcoxia is more selective."
- **Naproxen comparison.** The relative risk of CV events with Arcoxia was 1.7 vs. naproxen – which is fairly comparable to the 2.0 relative risk of Vioxx vs. naproxen in the VIGOR trial. Dr. Sean Curtis, Director of Clinical Research for Merck, said, "In terms of a signal, we acknowledge and see a difference in events rates vs. naproxen. The so-called signal observed (with Vioxx) in APPROVe was vs. placebo and was not observed until after 18 months of exposure…so the Arcoxia data to me are consistent with a cardioprotective effect of naproxen, not a negative effect of Arcoxia."

Merck's Dr. Curtis made these other points about Arcoxia:

- "Arcoxia is molecularly distinct from other compounds, and, based on the development program, it has unique properties."
- "All these drugs (Cox-2s), despite the chemical entity/structure, functionally inhibit Cox-2…but they are all different structurally and…you shouldn't, a priori, apply the safety findings of a drug in a class to other drugs in a class."
- "We presented a pooled analysis of all CV safety data (on Arcoxia)…and in that analysis, we show similar rates of confirmed thrombotic events (all CV events)…They are similar for Arcoxia, placebo, and non-naproxen NSAIDs…There is a decrease in (CV) event rates on naproxen vs. Arcoxia, and we've seen that with other Cox-2 inhibitors – Vioxx and lumiracoxib – so we have data from three compounds that show a similar pattern vs. naproxen…Naproxen could be acting like aspirin in reducing (CV) events…The rates of confirmed (CV) events vs. diclofenac are very similar as well as to placebo…The outlier is the comparison to naproxen, and there is a plausible explanation for that."

A poster presentation at the ACR meeting on the large (7,111-patient), one-year, randomized, double-blind EDGE trial did little to settle this issue. The trial met its primary endpoint of fewer GI events than the NSAID diclofenac, and there was no difference in CV risk between Arcoxia and diclofenac.

1-Year Results of the EDGE Trial of Arcoxia

Measurement	Arcoxia n=3,593	Diclofenac n=3,518	p-value
Discontinuations Due to			
Any cause	40.5%	45.8%	---
Lack of efficacy	9.7%	10.6%	---
Adverse events	18.2%	22.9%	---
Primary endpoint: GI adverse events	~ 8%	~ 15.5%	<.001
GI adverse events (as a rate per 100 patient years)	9.41	19.23	<.001 (relative risk 0.5)
Clinical serious adverse events	8.3%	8.7%	---
Edema-related adverse events	0.9%	0.7%	.435
Hypertension-related adverse events	2.3%	0.7%	<.001
Hepatic adverse events	0.3%	5.2%	<.001
Cardiac and Cerebral Event Rate within 14 Days of Treatment Discontinuation			
All cardiac events	0.97	0.73	---
AMI	0.68	0.42	---
Sudden cardiac death	0.07	0.04	---
Cardiac events in unstable angina patients	0.22	0.27	---
Cerebrovascular events	0.25	0.27	---
Peripheral vascular events	0.11	0.15	---
Cardiac and Cerebral Event Rate within 28 Days of Treatment Discontinuation			
All cardiac events	0.96	0.77	---
AMI	0.65	0.51	---
Sudden cardiac death	0.07	0.04	---
Cardiac events in unstable angina patients	0.24	0.26	---
Cerebrovascular events	0.27	0.29	---
Peripheral vascular events	0.14	0.29	---

Merck has others trials underway that may shed more light on the CV safety of Arcoxia, but they still may not be definitive since the trials are not placebo-controlled. Dr. Curtis said, "When we combine EDGE with other studies ongoing, we will have >35,000 additional patients beyond the development program, and many will be treated >18 months and some >3 years…So there is a mechanism to continue to assess safety…and we will have CV safety data from three studies in 35,000 patients, with the goal that Arcoxia is similar to diclofenac in terms of CV safety. We feel the existing development plans will clearly provide a large amount of safety data." These trials include:

- **EDGE-2.** This has a similar design to EDGE, but it is in 4,000 RA patients. The results are due about the same time as the MEDAL results.

- **MEDAL.** This is a large trial (23,500) patients, but 40%-50% have dropped out, though a researcher said this was not due to the withdrawal of Vioxx. MEDAL is not expected to reach its event-driven primary endpoint – CV safety – until early 2006.

Another poster at ACR reported on an open-label, six-week, single-center, 22-patient, U.K. study (sponsored by Merck) which found that Arcoxia decreases the need for biologic therapy in ankylosing spondylitis, but has no effect on MRI results.

Measurement	Baseline	6 weeks	Implications
Primary endpoint #1: 50% decrease in BASDAI	---	41%	Nss
Primary endpoint #2: Absolute decrease of 20 mm (2 cm)	5.8 cm	3.0 cm	Met
Secondary endpoint #1: % of patients with ASAS20	---	64%	---
Secondary endpoint #2: number of patients with MR lesions at sacroiliac and lumbar spine	---	N/A	No effect
Withdrawals	2 patients (1 for lack of effect, 1 for side effects)		
Side effects	2 edemas		

NOVARTIS'S Prexige (lumiracoxib)

Prexige (lumiracoxib) is a highly selective, second-generation Cox-2 inhibitor that Novartis is developing for arthritis and pain management. In late October 2004, Novartis announced that the FDA filing of Prexige is being delayed until 2007, a year later than previously expected.

In September 2003, the FDA said that before a decision on the approvability of Prexige could be made, Novartis had to submit:

1. The results of the TARGET trial comparing Prexige to naproxen and ibuprofen in 18,325 patients. This trial showed no statistically significant increase in CV risk, and a more favorable blood pressure effect profile vs. the two NSAIDs.
2. Additional data in hip osteoarthritis. This trial is ongoing.
3. Additional data in acute pain.

The assumption appears to be that the outlook for this Cox-2 inhibitor has worsened since the withdrawal of Vioxx, but Novartis researchers made a case for Prexige having less CV risk than Vioxx.

On the negative side:

- **Selectivity.** It is the most selective of all the Cox-2s.
- **FDA.** Experts believe the FDA will take a cautious approach to all new Cox-2 inhibitors.
- **Signal.** Prexige showed a CV signal in TARGET. A Merck researcher (sic) said, "In the TARGET data, the relative risk for cardiovascular event with lumiracoxib was 1.7 vs. naproxen. The relative risk for etoricoxib (Merck's Arcoxia) was 0.83, suggesting other NSAIDs, not just Cox-2 inhibitors may have some CV event rate."

On the positive side:

- **Half-life.** Prexige has a short half-life (4 hours), compared to 17 hours for Vioxx and 22 hours for Arcoxia.
- **pH.** It is the only acidic Cox-2 (pH 4.8), which makes it more like an NSAID in this respect.
- **Attributes.** In contrast to the other coxibs, Prexige is not a tricyclic, is not neutral, and has a sulfa group.

Prexige is already approved in the U.K. for the short-term relief of moderate to severe acute pain associated with primary dysmenorrhea, dental surgery, and orthopedic surgery. It is expected be approved in the rest of Europe during 2005.

The FDA Perspective

Experts are worried the FDA will be tougher on approvals of all drugs, particularly those in classes where safety questions have previously been raised, post the Vioxx withdrawal. One doctor suggested the FDA would take a "once burned, twice shy" approach and may require larger patient numbers. He did not think there is any increased risk (of withdrawal) for existing TNFs, but he pointed out that the lymphoma risk placebo over all the TNF trials is zero. As a result, he is "concerned in the back of my mind about it (lymphoma), but it is not in the front of my mind – now."

Dr. Janet Woodcock, Acting Deputy Commissioner for Operations at the FDA, reviewed coxibs and CV safety in a special session at ACR. Dr. Woodcock's general comments included:

- "Coxibs are among the most toxic drugs for a non-life threatening indication. They have hepatotoxicity, CV toxicity, renal toxicity, etc."
- "Differences in the toxicity profile among traditional NSAIDs have not been definitely shown."
- "We are far from understanding the complex mechanisms that may lead to this (CV risk)…I doubt it's one single mechanism alone."

Dr. Woodcock cited several difficulties in evaluating the CV risk of coxibs:

- Generally, long-term placebo-controlled trials can't be done in arthritis.
- Placebo-controlled data are the most interpretable because the CV effects of the comparators are not established.

- Suspicions of CV toxicity means trials in high risk groups need careful scrutiny – "because of the ethics."
- Higher risk groups take aspirin – and this often confounds the results.
- Many studies lack statistical power to detect the event rates seen in APPROVe.

On the outlook for other coxibs, Dr. Woodcock said, "Premarket requirements normally don't include an exhaustive evaluation of every possible adverse event…The FDA will have to look at the size of the safety database, etc., for the future for these agents…However, we have trade-offs here in getting products on market and determining the adverse event profile…ICH guidances usually call for 1,500 patients total, including 300-600 for over six months and 100 for 12 months. This is not sufficient for the kind of side effects (with Vioxx)…Frequently, the size of the premarket safety database is determined by the efficacy trial needs, not by what you want to know about safety…Class-specific concerns can affect the need for testing."

On Pfizer's Celebrex (celecoxib), Dr. Woodcock commented, "VIGOR (a Vioxx trial) showed an increased CV event rate. CLASS (a Celebrex trial) did not show an increased rate – but the event rate was quite low in the placebo arm…There are ongoing studies with celecoxib, and the FDA is very interested in these…There are two ongoing colon polyp trials that are fully enrolled…Both DSMBs get data updates and have issued statements that they are aware of the Vioxx withdrawal and have determined there is no indication for stopping these trials. These DSMBs meet again in late fall, and we will get an update at that time."

Dr. Woodcock also pointed to three studies that appear to indicate Celebrex is safer than Vioxx:

1. A retrospective cohort study in 2002 which found an increased CV risk with Vioxx over ibuprofen, naproxen, and Celebrex.
2. A new case control study in 2004 in patients over age 65 found a CV odds ratio of 1.17 for Vioxx and 0.95 for Celebrex.
3. A randomized clinical trial comparing Vioxx and Celebrex in hypertensive OA found more edema and a more pronounced blood pressure change with Vioxx over six weeks.

On Pfizer's Bextra (valdecoxib), Dr. Woodcock commented, "An increased rate of CV events has been reported in high risk (CABG) patients vs. placebo, so, in an acute setting here is another case of a increased CV event rate observed. Valdecoxib can increase blood pressure and lead to edema as well."

On Novartis's Prexige (lumiracoxib), Dr. Woodcock said, **"**In the TARGET trial of OA patients over age 50, there was no CV difference overall, but when we looked at a subgroup analysis, the rate of non-fatal MI was significantly higher for lumiracoxib vs. naproxen, even though the difference was not statistically significant…The (CV) rate for lumiracoxib was lower than for ibuprofen, but the statistical power to differentiate those two was fairly low."

The next steps the FDA will take include:

- Watching the outcome of the Celebrex trials ongoing.
- Exploring the Bextra data.
- Carefully scrutinizing new agents.
- Holding a public advisory committee meeting sometime early in 2005 to discuss CV safety as a step toward preparing new guidelines.

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