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FDA Advisory Panel Rejects Merck's Arcoxia Application

Cardiovascular Safety a Huge Concern
Door Still Slightly Ajar for New Cox-2 Inhibitors

The FDA's Arthritis Drugs Advisory Committee gave the thumbs down to Merck's Arcoxia (etoricoxib), a follow-on to Merck's Vioxx (rofecoxib), a Cox-2 inhibitor that was withdrawn from the market in 2004 due to an increased risk of heart attacks and strokes. The panel voted 20-1 on April 12, 2007, that the FDA should not approve Arcoxia. This makes it highly unlikely that the FDA will approve Arcoxia, but a final FDA decision is not expected until April 27, 2007.

Like Vioxx, Arcoxia is a Cox-2 inhibitor. The only Cox-2 inhibitor still on the market in the U.S. is Pfizer's Celebrex (celecoxib). Like Vioxx, Pfizer's Bextra (valdecoxib) was taken off the U.S. market in 2005 due to cardiovascular safety concerns. Merck is seeking FDA approval of Arcoxia for relief of the signs and symptoms of osteoarthritis (OA).

Before the vote, Dr. David Graham of the FDA's Office of Surveillance and Epidemiology in the Center for Drug Evaluation and Research (CDER) – and an early and leading critic of Vioxx – seemed to seal the drug's fate in the U.S. when he called it "a potential public health disaster," and warned, "We could have a repeat of what we had with Vioxx."

The panel rejected Arcoxia, determining that the benefits did not outweigh the risk. Dennis Turk Ph.D., acting panel chair, summed up the panel's view: "Although GI (gastrointestinal) effects and tolerability seem to be good, on the cardiac side there seem to be significant cardiac effects there." Other criticisms from the panel included questions about the drug studies themselves, including the comparator used, an older NSAID (non-steroidal anti-inflammatory drug). Panel members said they would have preferred to see a new Cox-2 inhibitor compared to drugs like ibuprofen and Celebrex.

The 21 voting members of the panel comprised a wide variety of experts, including seven rheumatologists, two epidemiologists, a pharmacist, four drug safety experts, two gastroenterologists, a statistician, a cardiologist, an anesthesiologist, a patient representative, and a consumer representative. The lone panel member voting to approve Arcoxia was Dr. Pankaj J. Pasricha, head of the GI division of the University of Texas Medical Branch in Galveston, who is a professor of internal medicine as well as a professor in the departments of pediatrics, anatomy, neurosciences, and biomedical engineering. He said he thought there is an unmet need for Arcoxia by certain patients who cannot tolerate other NSAIDs.

The panel generally concluded that:

- Arcoxia has a similar risk of heart attacks and cardiovascular (CV) problems as other non-selective NSAIDs.
- Merck did not demonstrate an unmet need for Arcoxia.
- Head-to-head trials comparing new Cox-2 inhibitors to ibuprofen and other NSAIDs are necessary.
- The benefits of Arcoxia did not outweigh the risks.

Still hope for other Cox-2 inhibitors

The cardiovascular safety of Arcoxia was a huge concern to panel members, but the FDA held the door slightly ajar for new Cox-2 inhibitors. The FDA said the vote doesn't mean other Cox-2 inhibitors in development will automatically get the ax. An FDA official told reporters that the agency would consider new Cox-2 inhibitors if the benefits outweigh the risks.

At a news conference after the vote, Dr. Robert Meyer, director of the FDA's Office of Drug Evaluation II, said, "We got very clear advice from the committee both in the discussion and in the vote itself…As I read the advice, it seems the advice applies to future coxib agents as well…If it were just another product that had the same level of risk as those out there now and no unique benefit to drugs out now, there is not sufficient reason to approve such a product unless there was some unique role defined."

Asked what the vote says to companies developing other Cox-2 inhibitors, he said, "Did we think the vote suggested that head-to-head type data would be needed for new drugs in this class? In many ways the FDA was already there. The data we heard today had head-to-head studies – whether (or not) they were the right studies…I think what I heard from the committee today is the suggestion that just looking like one of the end sets in terms of CV safety, with the exception of naproxen, may not be enough. More may be needed, in the committee's opinion. A head-to-head trial with specific results might be a better way to answer it."

Asked whether the advice about this class of drugs might extend to all drugs that are regulated, particularly with regard to me-too drugs, Dr. Meyer said, "We certainly heard that kind of suggestion from some in the public to the FDA before, but we're talking about a richly populated class of drugs. There are a lot of NSAIDs…Yes, we have a fairly dire but unusual CV risk. The tradeoff for having a new choice – if it's not different in terms of risk or benefit – didn't seem favorable. But I don't think that would broadly apply to all classes of drugs, especially in cases where there are very few drugs available."

Asked if he was saying that any future NSAID would have to show superiority to naproxen, Dr. Meyer said, "What I was trying to characterize was the advice as I heard it, not necessarily what the FDA's standpoint would be. I heard that, for this specific drug, a 30 mg dose comparison to naproxen might be a good idea. Whether that would apply to all drugs, I'm not sure I heard that. For example, a future coxib might go head-to-head with ibuprofen. That kind of data setup would be reassuring to many people."

Asked why the FDA held the hearing if it was already so forceful in its characterization of the drug's risk, Dr. Meyer said, "It may have seemed that way, but I can assure you that I did have a fair amount of uncertainty coming to this day."

Will the FDA make its decision by the PDUFA date, April 27, 2007? Dr. Meyer said, "Due dates are targets and are supposed to be hit 90% of the time…It is our intent to meet the due date."

Asked how the various NSAIDs and Cox-2 inhibitors compare on safety, Dr. John Jenkins, director of the FDA's Office of New Drugs in CDER, said, "The memo we did in 2005 (suggested) that the CV risk for naproxen is lower than other agents. We don't have adequate data to rank order. You heard a lot about diclofenac, but you didn't hear about the (other) agents out there. As we think about this class of drugs, we're handling this as a class effect. There is some suggestion that naproxen may have a lower risk than others in the class. They all have a boxed warning, and they all have a boxed warning for GI risk. We'll be looking at emerging data as it comes forward, but I don't think we've changed substantially from 2005." Dr. Meyer added, "There is not a lot of controlled data from these products. Pfizer is doing a comparative study – celecoxib against some other NSAID – but I think that, given what we know, we are comfortable that although naproxen may have a different magnitude of risk, they are risks that can be well described."

THE FDA'S PERSPECTIVE

The FDA case was that there is a class effect for an increased risk of adverse CV events with Cox-2 inhibitors. In background documents, the FDA said that NSAIDs (which includes Cox-2 inhibitors) should be approved for OA patients ***only if they fill an unmet need for a certain group of patients who have no safer options***. The FDA contended that Arcoxia had similar risks of heart attacks and CV problems compared to another painkiller, diclofenac. The FDA reviewers also said that patients on Arcoxia dropped out of the studies at a higher rate because of complications related to high blood pressure. The FDA wrote, "A new product that appears to have an increased overall risk profile for CV disease, particularly beyond that seen with other drugs in that class, would not be appropriate for marketing approval unless the product fills an unmet need for a particular patient population that has no relatively safer approved products available to them, and provides a reasonable risk to benefit balance for that patient population."

The key findings were:

- The risk for thromboembolic and CV events was comparable for Arcoxia and diclofenac.
- Arcoxia appears to have less CV risk than non-naproxen NSAIDs, greater risk compared to naproxen, and greater risk vs. placebo, but the number of events and duration of exposure were much smaller than in Arcoxia's three randomized MEDAL trials.
- Common adverse events were typical for an NSAID.
- The Agency did not agree with Merck's choice of a primary CV safety endpoint, confirmed thrombotic events.
- Arcoxia was associated with a significantly higher risk of renovascular events, but most patients who had renovascular events did not develop confirmed APTC (Antiplatelet Trialists' Collaboration), confirmed thrombotic, or arterial events. For those subjects with renovascular events, 1.6% of subjects also experienced an APTC event, 2.4% of subjects experienced confirmed thrombotic events, and 2.04% of subjects developed confirmed arterial events.

Dr. Bob Rappaport, director of the FDA's Division of Anesthesia, Analgesia and Rheumatology Products (DAARP) in CDER, told the panel, "There has been increased scrutiny of the Cox-2 selective products and indeed all of the NSAIDs …While there are still many unanswered questions regarding the CV and GI toxicity of these products, there is enough evidence that the Agency is able to define the requirements for approval of any new products in this class…While (Arcoxia) may provide some additional benefits, it may also have some increased associated risks. Determining exactly how to weigh the benefits and risks…is challenging…(The final question is) whether you believe the risk:benefit balance for Arcoxia is adequate to support the product's approval."

Dr. Robert Shibuya, DAARP's medical officer, told the panel that Arcoxia is effective at 30 mg and 60 mg per day, and GI safety looks good. However, he said results are mixed for renovascular and CV safety. He said that the six pertinent Phase II OA studies were very similar in design, and the treatment effect size is relatively the same. He discussed the Arcoxia MEDAL program, which had a large population (~35,000 patients) with substantial follow-up. The non-MEDAL database, by comparison, was very heterogeneous. It comprised 18 conventional Phase I-III studies in ~4,500 OA, rheumatoid arthritis (RA), ankylosing spondylitis (AS), and chronic discogenic low back pain (CDLBP) patients.

Efficacy summary

- One Phase II clinical trial shows some evidence of dose response between 5 mg and 60 mg, with wide confidence intervals, after six weeks of treatment. The differences between doses diminishes as the study progressed beyond six weeks.
- Arcoxia is effective at doses of 30 mg and 60 mg per day.
- Cross-study comparisons do not show evidence of added benefit for the 60 mg dose.

Safety summary

- **CV thromboembolic events**
  - As assessed by relative risk, the pooled MEDAL data show comparable CV risk vs. diclofenac.
  - The risk for Arcoxia (compared to diclofenac) could be as high as 2,300 excess events per million patient-years.
  - The non-MEDAL database suggests that Arcoxia is inferior to naproxen.
- **Renovascular safety**
  - Arcoxia 90 mg causes more hypertension, edema, and congestive heart failure (CHF) than diclofenac.
  - Arcoxia 60 mg causes more hypertension and slightly more edema and CHF than diclofenac.
  - Compared to other NSAIDs (celecoxib, ibuprofen, and naproxen), Arcoxia 30 mg and 60 mg appear mixed for renovascular safety, but this conclusion was described as "less robust" due to the relatively low exposures compared to diclofenac.
- **GI events**
  - For medically significant upper GI events, Arcoxia approximates diclofenac and appears to be superior to naproxen.
  - For non-serious GI-related symptoms, Arcoxia is superior to diclofenac and naproxen.

The FDA's Dr. Graham was an early Vioxx critic, and he didn't support Arcoxia approval. He argued that Merck's entire premise – comparing Arcoxia to diclofenac – is not appropriate for assessment of CV risk and said that Arcoxia probably results in substantial CV risk. Looking at prescription non-coxib NSAID use in the U.S. from 2000-2006, Dr. Graham said that ibuprofen was the most used, followed by naproxen, with diclofenac rarely used in the U.S. at all. He said that diclofenac increases CV risk and naproxen does not, adding, "There is a chance that ibuprofen can increase risk, but that is unknown and is probably somewhere in the middle." He estimated that Arcoxia increases the CV risk 2.7-fold compared to naproxen.

Dr. Graham made a number of arguments, including:

- **Testing.** Dr. Graham said that the FDA's requirement for approval of a new drug is "adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling." He contended that Merck had not met that requirement.

- **Comparator.** Dr. Graham called diclofenac an inappropriate comparator and recommended that any new coxib be compared to naproxen + a proton pump inhibitor (PPI) for upper GI and CV outcomes. He said, "I'd also include celecoxib in all the trials. It has the most data to suggest that its CV effects are non-existent. It has a lot of advantages…Wouldn't you be looking for superiority or at least equivalence before you go approving another Cox-2 selective inhibitor?" He suggested that the committee make recommendations for appropriate designs for future studies, stressing his concern about the Arcoxia studies. He later added, "There is no increased risk of CV outcomes with naproxen."
- **CV risk.** Arcoxia probably confers substantial increase in CV risk and called this an "enormous public health and population consequence."
- **Efficacy.** He argued that Arcoxia is no more effective for pain relief than NSAIDs.
- **Gastroprotection.** The combination of naproxen + a PPI is equivalent to coxibs for gastroprotection but has a substantial CV safety advantage and is substantially less expensive.
- **Dose.** He particularly criticized Merck's request for approval to market Arcoxia 60 mg, saying, "There is no difference in pain relief between the 30 mg and 60 mg doses. Why ask for disaster by approving the 60 mg dose? There are no data on the 60 mg strength. (Merck) is asking you to blindly accept that the CV risk isn't present. We don't know that for a fact. 30 mg might be close to 60 mg because the level of pain relief with these drugs is similar."

Dr. Graham told the panel, "(Merck was) wrong with respect to diclofenac. They are wrong with respect to naproxen. Additionally, naproxen doesn't interfere with the beneficial effects of aspirin. Further, an NSAID plus a PPI appear to be equivalent to coxibs for upper GI outcomes. There is no added benefit of coxib use that is apparent to me."

Based on a relative risk of 2.72 for Arcoxia vs. naproxen, he estimated that:

- 1 in 18 males per year aged 65-74 would have an adverse CV event on Arcoxia.
- The number needed to harm (NNH) for Arcoxia is 147 person-years.
- 6,800 extra APTC events per million person-years would occur with Arcoxia use.

GI Outcomes in Pooled MEDAL Program

Event classification	Arcoxia		Diclofenac	
	Event rate	Hazard ratio	Event rate	Hazard ratio
Upper GI outcomes				
Confirmed/complicated	0.45%	0.30	0.47%	0.32
Confirmed/complicated and not complicated	1.01%	0.67	1.42%	0.97
Confirmed and unconfirmed/ complicated	0.59%	0.39	0.71%	0.48
Confirmed and unconfirmed/ complicated and not complicated	1.15%	0.76	1.63%	1.11
Lower GI outcomes				
Confirmed/complicated	0.44%	0.29	0.50%	0.34
Confirmed/complicated and not complicated	0.48%	0.32	0.56%	0.28

Summary Statistics for CV Outcomes (Pooled MEDAL Program)

CV outcomes	Drug	Number of patients	Number of patients with confirmed APTC event/patient-years	Hazard ratio	Relative risk
Primary analysis: Pre-protocol approach	Arcoxia	16,819	216 / 25,851	0.84	0.96
	Diclofenac	16,483	216 / 24,787	0.87	
Secondary analysis: Within 14 days (mITT)	Arcoxia	17,412	231/ 26,402	0.87	0.96
	Diclofenac	17,289	232 / 25,416	0.91	
Sensitivity analyses					
Within 28 days (mITT)	Arcoxia	17,412	237 / 27,059	0.88	0.95
	Diclofenac	17,289	239 / 26,068	0.92	
All events (ITT)	Arcoxia	17,412	332 / 39,894	0.83	1.02
	Diclofenac	17,289	325 / 39,623	0.82	

Specific Upper GI Events in Pooled MEDAL Program

Event	Arcoxia		Diclofenac	
	Confirmed/complicated events	Confirmed/complicated and not complicated events	Confirmed/complicated events	Confirmed/complicated and not complicated events
Ulceration	38	175	32	249
Perforation	5	5	11	11
Obstruction	2	2	2	2
Hemorrhage	70	78	71	76

MERCK'S PERSPECTIVE

Merck argued that Arcoxia, which is already approved in 63 countries outside the U.S., is safer than Vioxx, is no less safe than approved NSAIDs, and has no novel toxicities that would prevent its inclusion in the approved NSAID armamentarium. The company also said that Arcoxia is gentler on the stomach than some popular pain drugs and claimed there is an unmet need for the drug, despite the variety of therapies available to OA patients.

Merck said that Arcoxia, at doses of 30 mg and 60 mg, provides a treatment option for OA with:

- Comparable efficacy to traditional and Cox-2 selective NSAIDs.
- A superior GI safety and tolerability profile, compared to traditional NSAIDs, that is maintained with PPI use.
- A safety and tolerability profile consistent with that of traditional and Cox-2 selective NSAIDs.
- An overall favorable risk:benefit relationship.

Merck's president, Dr. Peter Kim, told the panel, "All options come with some risk. For NSAIDs, while often highly effective for managing the symptoms of OA, their labels currently include warnings regarding both GI and CV risks. It is only through well-controlled clinical trials that the unique benefits and risk…can be defined. We initiated the MEDAL program for Arcoxia in 2002. The MEDAL program is the largest and longest controlled clinical trial specifically designed to assess the CV safety of a treatment in patients with arthritis. More than 34,000 patients were enrolled in these trials with more than 17,000 patients receiving Arcoxia …for a mean duration of 18 months. There were more than 26,000 patient-years of exposure to the drug…We at Merck believe Arcoxia represents a valuable treatment option for patients with OA. We'd like to emphasize that there is more long-term safety data from controlled clinical trials in terms of patient-years of treatment for Arcoxia than for any other NSAID. We hope you will conclude that patients in this country should also have access to this treatment option."

Dr. Scott Korn, Merck's executive director of regulatory affairs, told the panel, "Patients with OA want and deserve additional options…It (Arcoxia) would be a valuable treatment that addresses that unmet need. Arcoxia has a favorable risk:benefit profile. Arcoxia has improved GI safety and tolerability even in those patients on a proton pump inhibitor. The thrombotic CV safety profile has been well characterized and is consistent with non-naproxen NSAIDs."

Dr. Grant Cannon, a rheumatologist from the University of Utah, also spoke on behalf of Merck, telling the panel doctors need Arcoxia in their arsenal. He said that OA is the most common musculoskeletal disease in the U.S., affecting 12.1% of the general population, or more than 21 million people. He said that non-selective NSAIDs and Cox-2 selective inhibitors are the most used treatments for OA, adding, "No therapy is either universally effective or universally well-tolerated…Each option has its own risk:benefit ratio…We need to expand the number of options available so that we, as physicians, can effectively treat our patients with this disease. There are currently many unmet needs and high levels of dissatisfaction (with current drugs)."

Dr. Cannon said that 73% of general practitioners and 63% of patients are not satisfied with their current treatment options, with lack of efficacy the most common reason for changing therapies, followed by GI intolerance. He pointed out that switching is less common with selective Cox-2 inhibitors. He concluded, "The addition of new agents, even with similar mechanisms of action, has the potential to provide additional relief for many OA patients."

Dr. Sean Curtis, Merck's executive director of clinical research, gave an efficacy and safety review of Arcoxia. He said, "The efficacy demonstrated with Arcoxia is comparable to NSAIDs. Naproxen has shown lower rates of CV events compared to Arcoxia, whereas Arcoxia is comparable to diclofenac. The GI safety and tolerability profile is superior to traditional NSAIDs."

He outlined seven of the clinical studies that have involved Arcoxia and included 3,897 patients, including one dose-ranging study and six Phase III studies. Two of the Phase III studies compared Arcoxia 60 mg to naproxen 500 mg BID, two studies compared Arcoxia 30 mg to ibuprofen 800 mg TID, and two compared Arcoxia 30 mg to Celebrex 200 mg QD. He said the studies found:

- In an OA dose-ranging study 60 mg Arcoxia was more effective than 30 mg.
- Arcoxia 60 mg was comparable to naproxen 1000 mg.
- Arcoxia 30 mg was comparable to ibuprofen 2400 mg and Celebrex 200 mg.
- Arcoxia was effective for treating OA symptoms.

Dr. Curtis described two complementary evaluations of Arcoxia safety: (1) The MEDAL program, which comprised three studies, and (2) the Arcoxia Development Program (n=10,033) which totaled 18 studies, including 11 studies in OA, 3 studies in RA, 3 studies in chronic low back pain, and 1 study in ankylosing spondylitis.

Arcoxia Development Program Thrombotic CV events

Comparison	Relative risk	Patient-years	Events
Arcoxia vs. placebo	1.07	1,260	14
Arcoxia vs. non-naproxen NSAIDs	0.73	2,464	20
Arcoxia vs. naproxen	1.70	4,207	48

The MEDAL program, which began in 2002, compared the thrombotic CV safety profile of Arcoxia to a traditional NSAID in arthritis patients. Dr. Curtis said that diclofenac was chosen to be the comparator because "it is the most widely prescribed NSAID worldwide, and it does not interfere with the antiplatelet effects of aspirin." Dr. Curtis said that the thrombotic CV results were consistent across endpoints, with no differences observed in MIs and ischemic strokes. He said that rates for fatal MI were low, but numerically higher with diclofenac.

Dr. Curtis said that the 2006 meta-analysis of randomized controlled trial (RCT) data supports the 2005 FDA conclusion: Available data is consistent with a class effect of increased thrombotic CV events for both Cox-2 selective and non-selective NSAIDs. He added, "Observational data do not clearly establish the magnitude of CV risk with diclofenac… No difference was observed in the rates of vascular events between Cox-2 selective inhibitors and diclofenac or ibuprofen…We feel…that Arcoxia was the right choice in 2002 and remains a scientifically valid and appropriate choice even today."

Other MEDAL and development program conclusions included:

- **CV safety.** Arcoxia was non-inferior to diclofenac in thrombotic CV event rates. Arcoxia had consistent thrombotic CV results across endpoints and analytical approaches, across multiple subgroups, and across a range of CV risk factors.
- **Mortality.** Arcoxia had similar overall mortality to comparator NSAIDs.
- **GI effects.** Upper GI clinical events included perforation, obstruction, bleeding, and ulcer, but there were fewer upper GI events with Arcoxia.
- **Hypertension.** Hypertension effects were observed for Arcoxia 30 mg and 60 mg.
- **Edema.** Edema was similar to traditional NSAIDs.
- **Congestive heart failure (CHF).** This was similar with Arcoxia to traditional NSAIDs.
- **Blood pressure.** The mean change in systolic blood pressure (SBP) in MEDAL was ~1.6 mmHg higher with Arcoxia 60 mg than diclofenac.
- **Discontinuations.** In the 60 mg Arcoxia cohort in MEDAL, discontinuations due to hypertension were higher with Arcoxia 60 mg, but edema and CHF were similar.

Dr. Curtis said that post-approval activities would include adverse event reporting and other standard pharmacovigilance activities, education for patients and physicians, and drug utilization studies. He indicated Merck had no current plans for direct-to-consumer (DTC) advertising until after physicians are aware of the drug's "key attributes." In conclusion, Dr. Curtis claimed that Arcoxia has a favorable benefit:risk profile in OA, with robust efficacy with QD dosing, provides dosing flexibility based on individual patient needs, and at 30 mg is comparable to NSAIDs, while 60 mg may provide additional benefit in some patients. He emphasized Arcoxia's improved GI safety and tolerability vs. traditional NSAIDs, ulcer reduction, improved GI tolerability, and a favorable hepatic safety profile.

Rate of Observed MIs and Ischemic Strokes in MEDAL Program

Measurement	Arcoxia n=16,819	Diclofenac n=16,483
Total patients with composite endpoint	1.24	1.30
Cardiac events	0.71	0.78
Non-fatal MI	0.41	0.42
Fatal MI	0.02	0.07
Cerebrovascular events	0.34	0.32
Non-fatal ischemic stroke	0.21	0.22
Fatal ischemic stroke	0.02	0.01
Peripheral vascular events	0.21	0.22

Upper GI Safety in the Arcoxia Development Program and MEDAL Trials

Side effect	Relative risk	Patient-years	Events
Arcoxia vs. naproxen			
Overall upper GI events	0.41	4,203	79
Complicated events	0.53	4,212	34
Arcoxia vs. diclofenac			
Overall upper GI events	0.69	51,775	422
Complicated events	0.91	51,843	160

PUBLIC SPEAKERS

A consultant to plaintiffs in Vioxx litigation, Dr. David Egilman of Brown University, came down hard on Merck and Arcoxia, saying, "As Ronald Reagan said, 'Fool me once (Vioxx), shame on you. Fool me twice (as in Arcoxia), shame on me'…Cox-2s increase mortality overall and may cause Alzheimer's." He called Merck's safety data unreliable and claimed that Arcoxia is associated with more hypertension, renal complications, CHF, strokes, MIs, and arrhythmias.

Dr. Egilman said that there are no data from Merck on atrial fibrillation (AF) for 60 mg: "They say AFs are comparable. My suspicion is that means there are more events on Arcoxia, but it's not statistically significant. I could be fooled." Dr. Egilman claimed that Merck habitually presented "bogus numbers," going as far as to point out a Merck physician sitting in the room whom he said had admitted playing with the numbers. He called Merck's actions "cagey," referring to some data published in a paper, but not included in studies. "Beware of people who present bogus numbers and are willing to repeat them over and over again in forums like this…It's a death warning if you approve this drug."

Public Citizen Health Research Group director Dr. Sidney Wolfe told the panel to "shut the door" on Arcoxia and what he called similar "fatally flawed" drugs. He also called on Merck to pull Arcoxia from the market in the rest of the world where it is sold. Dr. Wolfe criticized the use of diclofenac as a comparator, saying "It's clear that the choice of a comparator makes the world of difference. Although Merck said that the choice of diclofenac is because it's the most prescribed drug in the rest of the world, that is not the case here (in the U.S., where) it's one of the least prescribed drugs. It doesn't make a lot of sense to use that as a comparator…I think the (Arcoxia) study was unethical because it followed the knowledge that naproxen had a much lower CV risk than the Cox-2 drugs, and this (Arcoxia) is a minor variation of Vioxx."

Dr. Wolfe also said, "If Vioxx were coming up for approval vs. naproxen, would it get approved? The answer is no. Then why should the similarly dangerous off-spring of Vioxx be approved? And like its parent, Vioxx, it has been shown to have increased CV risk compared to naproxen…How can the approval…be justified? There is no basis for recommending the approval. Thousands – probably tens of thousands of patients – have probably had needless heart attacks because they took one of the Cox-2 drugs…It's time to shut the door on this dangerous class of Cox-2 drugs. The idea that there may be some patients who benefit is just not good enough as a basis for its approval. It doesn't fill an unmet need…I urge prompt removal of Arcoxia from the market in the 60+ countries where it is posing risks to people using the drug…It's time to stop messing around with people's health. The FDA should stop encouraging other companies from doing any more clinical trials on these drugs. They are fatally flawed drugs."

PANEL DISCUSSION

The key issues for the panel were safety, trial design (including why diclofenac, which is little-used in the U.S., was the comparator), presentation of study results, and whether there is an unmet need for the drug. The panel also worried that there were not enough data on the recommended 30 mg dose. Panel members agreed that there is a class effect with Arcoxia, and that it causes increased CV problems. In addition, panel members asked Merck about CV safety, the difference between the 30 mg and 60 mg doses. They also questioned Merck's figures and criticized how the company presented the figures.

Subgroups. The panel chair wanted to know if he should pre-select certain patients for Arcoxia and whether the CV events in the trials underestimate what happens in the real world. A Merck official responded that patients with uncontrolled hypertension, Class III or IV CHF, or acute cerebrovascular or coronary events in the prior six months were excluded from the trials, "We feel it was real world or representative of a patient population that would be getting these therapies, but there are limitations to any clinical trial."

Unmet need. A panel membeer asked about Merck's contention that there is an unmet need for Arcoxia, "Since the product has been marketed in other countries, are there data on switching to the product?" A Merck official answered that there were no specific studies that have looked at patients switching to Arcoxia. A rheumatologist on the panel commented, "This is a weak argument about this crying need. I certainly don't give people all 20 (alternatives) to find out if they're going to respond to the 20th one after they've failed 19. A new drug has to have some reason that you'd put it in the top six of your rotation or it's not going to have much effect."

30 mg Arcoxia. A panel member asked about CHF with the 30 mg dose, and a Merck official responded, "The data for 30 mg come from the non-MEDAL portion of the program – the development program. Data for CHF with 30 mg are limited to the development program. It wasn't included as a dose in MEDAL."

- *Panel member:* "You've shown us a blithering number of slides, but…my concern is we've heard very little about the 30 mg dose. You have only 1,100 patients treated with the 30 mg dose, for not a clearly specified time. So you probably have far less data on the outcomes there. We were given outcomes with regard to efficacy and blood pressure changes, but we weren't given the thrombotic CV outcomes for the 30 mg dose. I was wondering if you had that data."
- *Merck:* "That does come from the development program …These are relatively rare events, and that is why we pooled the data. I agree it's important to look at dose. You see a dose trend in terms of GI effects (with 30 mg) which is not surprising...but (there is a) very limited amount of data…I think we'd have zero (complicated) events on the 30 mg."

Statistical analysis. A panel member asked how the adverse event adjudication – that a public speaker (Dr. Egilman) questioned – evolved, pre-hoc or post-hoc, regarding fibrillation. A Merck speaker said, "The adjudication of CHF data from the MEDAL program were adjudicated, and it came at the request of the data safety monitoring board (DSMB). They asked us near the end of the trial to implement a process to adjudicate CHF. So we took on the recommendation and their specific request was to adjudicate cases regarding hospitalization. At that point, we were well into the program. The investigators were still blinded completely. We implemented the following process: We looked at all eligible pre-specified CHF…We went to the investigators and set up pre-specified adjudication criteria. The committee reviewed the data, as they had been doing, and made independent adjudication of those data. There were at total of 124 cases. They were adjudicated in equal proportion." An FDA official said, "I did go back and check records, and we did at least on four occasions comment that we were concerned about the (trial) design with only one comparator – and it being diclofenac – because we were concerned."

Stroke. A panel member asked if stroke is more prevalent in patients with elevated blood pressure. A Merck official responded, "The primary result was that there was no difference in strokes and heart attacks in the composite (end-point). We looked at patients with a baseline history of hypertension, but…looking at all established risk factors for heart disease…we did not specifically look at post-randomization elevation in blood pressure."

Did the FDA get it wrong (with Cox-2s) in 2005? The FDA's Dr. Meyer said, "I don't think we got it wrong in 2005. Whether it needs to be rethought is an ongoing question, and we'd be happy to reconsider the general conclusions of that document over time as more data accumulates." A panel member responded, "I say you did get it wrong. I don't think it was the intent of those committee votes (in 2005) that we have a generic black box warning that didn't at least address what was known to be wrong at that point. I'm not sure you got it right then." Dr. Meyer retorted, "You're welcome to your opinion, and I'm welcome to mine as well."

Distribution and post-approval marketing. Despite repeated FDA comments that the panel should not consider restricted distribution for Arcoxia, some panel members continued to bring the topic up. A pharmacist asked Merck if it had considered marketing Arcoxia in a much more restrictive plan so that only patients most likely to benefit from the drug would receive it. A Merck official responded, "We feel we articulated the core elements of our risk management plan: Risk assessment and risk communication, including the core component, the product label…We're talking about education fundamentally based on the content on the label – aimed at physicians – talking about benefit and risks of the compound, and we're talking about class effect. These drugs do work in arthritis and this compound is efficacious."

Another panel member had this exchange with a Merck official:

- *Drug safety expert:* "I have a question about Merck saying it has no plans for DTC TV advertising at this time."
- *Merck:* "We're trying to describe an event-driven trigger. We have no plans for television advertising at this time. We want to make sure everyone is aware of the risk:benefit before we even consider…"
- *Drug safety expert:* "You will speed up the education process and you're going to do these surveys. The only good argument I've heard for no DTC is that it slows the adoption rate for the drug and allows you to accrue risk information. Are you going to have a registry? Do something special to accrue the risk information?"
- *Merck:* "We estimate 12-13 months before we have data to make assessment in terms of awareness. We do not have plans for a registry at this point…We are willing to discuss options."

Number needed to treat (NNT) and number needed to harm (NNH). Panel members were interested in these computations. The panel chair questioned whether Merck had calculated NNT and NNH, and a Merck official responded, "NNTs don't allow one to make decisions on an individual patient basis…We can calculate the NNT. It's 250-300 in terms of the MEDAL study vs. diclofenac. If we look at naproxen, it's something like 60. Here, naproxen and diclofenac are different. The NNT is smaller for naproxen."

- *Epidemiologist:* "You can also predict the number needed to kill. If you use the rate of 5% complicated GI events – and you use the favorable rate – 5% of complicated events lead to death. The number needed to treat is 1,200 to save one life. If you take the CV events…167 are needed to treat to cause one MI compared to naproxen. If you use the FDA's data, the number is much less than that…You (Merck) inflated your numbers in order to create a number that, to me, wasn't significant…I want to know what the real events were – not TIAs, not other things that didn't leave anyone with the risk of death. Can someone from the FDA provide that?"
- *Merck:* "We did show overall mortalities."
- *Epidemiologist:* "Please confine yourself to responding to my question…The number needed to kill was something like you treat 600, and you kill one person who would not have been killed if you hadn't had Arcoxia available to you. So, the tradeoff is about two to one. You kill twice as many people as you save. That's compared to naproxen, and that's using conservative estimations from the sponsor. The FDA has presented data showing a higher risk than that."
- *FDA official:* "For naproxen at 1,728 patient-years, we have 5 total deaths; 3 were CV, for a rate of 0.17. For Arcoxia, patient-years are 4,100, and there were 10 CV deaths, for a rate of 0.24. The CV thrombotic deaths are slightly different: 9 (deaths) with a rate of 0.22 for Arcoxia, and 2 with a rate of 0.12 for naproxen."
- *Epidemiologist:* "So it's a 1 per 1,000/year difference, which is almost exactly what I suggested. You would kill one person out of every thousand compared to naproxen."
- *Merck:* "In the MEDAL program there was no difference."

European experience. A panel member asked about use of Arcoxia in Europe, saying, "It's causing quite a lot of angst. They had 1,561 cases of upper GI complications between 2000 and 2005, and, in addition, they looked at the relative risk in patients who had nine different coxibs and traditional NSAIDs. The dramatic finding was that all the others pretty much had a risk of about 5 (indomethacin 7.2, Arcoxia 12). Then, when they looked at low-medium, and high-medium doses, all the low-medium doses of all 8 of the NSAIDs were ≤5, and Arcoxia was up at 12, being the most toxic for upper GI complications. When they used high doses, most of them

were all in <5 range, with indomethacin the highest, Arcoxia next, and naproxen next. My question is: Have you had reporting from Europe regarding upper GI toxicity?" A Merck official responded that it is difficult to make comparisons of products, "Patients who get Cox-2 inhibitors and in this case etoricoxib, are not, in fact, those who are most likely to have GI events."

Asked if they have done health economic analyses, a Merck official said, "The European agencies that approved Arcoxia did not require health assessment analyses." A panel member commented, "One of the most compelling arguments for this is that it helps people who aren't helped by other medications. This is comparable on average to other drugs. I mean, we could be helping the same people…Do you have any evidence such as a crossover study or experimental evidence to show that this (Arcoxia) helps people who aren't helped by current therapies?" The Merck official answered, "No, there have been no specific crossover studies. That doesn't take away from the clinical reality – the variability of response among agents. It's difficult to predict response in individual patients."

Non-responders. The FDA's Dr. Jenkins and a Merck official had an interesting exchange on non-responders:

- Dr. Jenkins asked if there are data showing that non-responders to one therapy, when re-randomized back to the therapy they failed or to the new agent, respond to the new agent, "Do you have any such data for Arcoxia or Vioxx where you've taken people who failed and then re-randomized them to see if you can see a difference in the effect?"
- *Merck:* "We haven't done that study, but we have robust data across subgroups in terms of maintenance of treatment effect."
- *Dr. Jenkins* asked why not.
- *Merck:* "The difficulties of defining non-responders."
- *Dr. Jenkins:* "That leaves us with nothing more than anecdotes. It would be nice to see some controlled data to show that people who don't respond to one respond to another."
- *Merck:* "Methodological limitations don't take away from patient satisfaction rates. The switching rates are real…The patients, the physicians, and numerous experts say this is the clinical reality of treating patients with arthritis."
- *Dr. Jenkins:* "As you talk about availability and what benefits the drug brings vs. risks, we keep hearing about anecdotes, but that's not the same as data that shows that people don't respond to one respond to another one and that would be powerful data to have to offset questions about increased risk."

PANEL DISCUSSION POINTS

The panel agreed that Arcoxia is part of a class effect, has a similar profile to other NSAIDs, and is perhaps worse than naproxen on side effects. A cardiologist said that, keeping in mind that there is an increased CV risk with Arcoxia, the decision came down to whether there is a clinical need for the drug.

FDA discussion point: Has the safety profile of Arcoxia been sufficiently characterized? Yes, the panel agreed.

Panel comments included:

- *Panel chair:* "(Merck is) suggesting starting at 30 mg. What's not clear is when you make the decision to switch to 60 mg."
- *Gastroenterologist #1:* "We know it (Arcoxia) is just as bad as the other NSAIDs and perhaps worse than naproxen. The data compared it to two other non-steroidals on the market today. The safety has been well-characterized…A lot of my patients, even on ibuprofen, say it's tearing them up. So, there is an unmet need for some patients who respond to a Cox inhibitor but without the dyspepsia. Not so much safety but tolerability. I think we should talk about that. That may represent the unmet need…I think complicated events are clear; there's no difference. But there's a lot of evidence that coxibs reduce dyspepsia significantly…I'm pointing out that there is a segment of patients who might need an alternative because of tolerability. You can argue that you can add a PPI. We're just talking about whether there's an unmet need."
- *Gastroenterologist #2:* "I can't comment on the CV effects, but I think it's more important than the GI effects. GI complications are important, particularly the ones that are complicated. As the sponsor knows, it's easy to find something when you look down the endoscope, but the important thing is how serious the complications are. With the dose response going up, I think it's very real. But when I vote, I have to balance it with the more serious CV effect. So, the advantage of a coxib is that it has less potential to cause GI problems…The serious problems are what we have to vote on. When you get into arthritis, you have many high-risk patients, so you have to balance the risks. I'd put CV first and GI second, even with the complications…As I keep going back and forth, questions exist about the heterogeneous population, the fact that it's hard to tease out, big differences in PPI and aspirin patients. When you put it all together, you look for a blockbuster or something that's giving us a little advantage. We're still arguing in GI whether coxibs are better or not, and until we can tease out something unique with this drug, I haven't seen data to tell me otherwise."
- *Pharmacist:* "If I could choose between a drug that causes hypertension and one that didn't, I would choose the one that didn't." (*The audience laughed at this.*)

- *Cardiologist:* "Everything we've seen is consistent with the class effect of coxibs. We can't compare this drug with the other coxibs, but it's consistent with the class effect and probably greater than what might have been seen with naproxen. In my mind there is an increased CV risk with this agent, and it comes down to determining whether there is a clinical need for this drug. That's what we're struggling with. We don't have strong data that there's a need for this drug in addition to what's already available. As for safety, I don't believe there's a difference between this and the other coxibs; they all increase CV risk."
- *Rheumatologist #1:* "I would want to see longer term data with 30 mg Arcoxia and, in particular, how long patients were able to stay on the 30 mg dose before there was a dose elevation. That's one of my concerns."
- *Rheumatologist #2:* "In OA we don't have good drugs. There is an unmet need. But there were no striking reasons to think this drug would cause less dyspepsia than others. I'm concerned only about the symptoms that can't be cured by stopping the drug, the ones that put you in the hospital or make you die."
- *Rheumatologist #3:* "This is not going to be a cheap drug for a long time. They've studied a million patients for a million years, so the third-party payors won't pay…That's a way of controlling distribution."
- *Asked by a panel member if the FDA could recommend approval with a variety of restraints*, an FDA official said, "I would not like to see a vote contingent on restrictive distribution. I don't think it's clear whether there is a specific patient population that could benefit from the drug that could be identified. Also, having a restricted distribution plan is difficult to impose on a drug. From a philosophical point of view, it should be restricted to those drugs where the drug has a restricted role for an important treatment, (i.e., thalidomide for leprosy). One can see other drugs like that, where they have a unique role in therapy. I don't think that a unique role for this drug has been defined. To the degree that we have some important questions about its risk:benefit; if those questions haven't been significantly answered I'd say vote yes or no. In my mind it should lead to a no vote. If you need more data to make the decision to recommend, then those data should be available beforehand, not afterwards. When a Phase IV study is done, particularly a multi-year study…you may be four or five years down the road…I want to steer people away from restrictive distribution."
- *Pediatrician:* "A qualified indication is not out of the question…It raises the question: Would it be appropriate to give an indication for OA for patients intolerant of GI side effects and who have low CV risk?"
- *FDA official:* "We heard comments about restricted distribution or access. You can have box warnings, second-line indications, and recommendations not to use it in certain groups of patients; but these are also very difficult for the agency to actually enforce. It's when you get to further tiers of restriction – certain training to prescribe the drug or a patient has to be registered in a program to get it. That's what we're talking about when we talk about restricted distribution. We're talking about a drug that warrants the risk the drug may have. We have trouble understanding why we would want restricted distribution unless it's really demonstrated benefit over available therapy. Labeling comments come after your yes or no for approval."

FDA Panel Vote

QUESTION: Do you recommend approval of Arcoxia for relief of the signs and symptoms of OA? 20 No, 1 Yes

Summarizing the panel discussion before the vote, the panel chair said that GI effects and tolerability seem to be good, but there seem to be significant cardiac side effects and that the panel was being asked to balance the positive GI effects of Arcoxia against the cardiac negative side effects. An epidemiologist on the panel added, "There is nothing special about this drug. It is no better than placebo. These drugs are not indicated for OA unless we determine that their CV risk is lower than it seems. This class and conventional non-steroidals just don't work well. These drugs are modestly effective at best, so I don't see any reason to test this and any others in its class ever unless we see that CV risk is really not increased."

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