FDA committees recommend naproxen as first-line therapy over coxibs

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The world watched as FDA committees made coxib recommendations

Gaithersburg, MD - The US **Food and Drug Administration** committees have formally recognized the cardiovascular and cerebrovascular risk of COX-2 selective agents. Members of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee voted overwhelmingly in favor of naproxen with a proton pump inhibitor as first-line therapy over coxibs, and most called for black-box warnings, additional physician and patient-education materials, and better postmarketing surveillance.

"One of the clearest signals from all of the trials is the relative safety of naproxen," **Dr Steven Shafer** (Stanford University VA Palo Alto Health Service Care System, CA) told **heart*wire***. "And many trials — in fact all of the trials — that compared drugs with naproxen consistently found improved safety with naproxen." When asked whether he personally would recommend the over-the-counter product, Shafer responded with a laugh, "I actually have it with me now. I took an informal poll among committee members at dinner," he added, "and all of them had brought an NSAID, and without exception, they brought naproxen — their NSAID of choice."

The panel voted unanimously in favor of recognizing the cardiovascular effects of the three COX-2 inhibitors available in the US — **celecoxib**, **valdecoxib**, and until recently, **rofecoxib**. All but one panel member voted in favor of the overall risk-to-benefit profile supporting the continued marketing of celecoxib (Celebrex®, Pfizer).

Panel okays celecoxib, but with stricter warnings

Recommendations for celecoxib:

- Initiate black-box warning.
- Halt direct-to-consumer advertising.
- Add educational materials.
- Call for lower 200-mg dose.

The committee as a whole decided that while celecoxib should continue to be available, stricter cautions are in order, including a strongly worded black-box warning about thrombotic risk and education materials such as a "Dear Healthcare Professional" letter and patient-education materials. The committees also talked about dose-dependent toxicity and tended to err on the side of doses of 200 mg. Several panelists also urged that direct-to-consumer advertising of celecoxib be halted.

Arthur Levin, an expert in health policy and a committee member representing consumers, was the one panelist who voted against the continued marketing of celecoxib. "It takes forever in this negotiated process to get the things in place that are recommended and then accepted by the FDA. I am very concerned about the time line," he said, noting that similar meetings raising concerns about Roche's **isotretinoin** (Accutane®) have been dragging on for at least a year. "Based on prior experience, you are not going to see this in the next couple of months."

Meeting chair **Dr Alastair Wood** (Vanderbilt University Medical Center, Nashville, TN) responded, "I think one of the jobs of the committee should be to provide a guideline for a time frame and light a fire under these guys." The other option, he added, could be to impose such severe restrictions on products that companies have an incentive to work to have them removed.

Speaking on behalf of the FDA, **Dr Robert Temple**, from the Office of Drug Evaluation, responded, "We're committed to making our decision on your recommendations about these products very quickly after this meeting, and we will do everything we can to implement whatever changes there are as quickly as possible — recognizing that there are sometimes certain logistical issues that have to be worked through — but we are committed to working as quickly as possible."

Divided over rofecoxib: Merck has decision to make

Recommendations for rofecoxib:

- Initiate stronger black-box warning than celecoxib.

- Prohibit direct-to-consumer advertising.
- Add educational materials.
- Cut dosing from 25 mg to 12.5 and virtually eliminate 50 mg.
- Commence patient informed consent (possibly).

The panel was split over whether or not the overall risk-to-benefit profile supports the renewed marketing of rofecoxib (Vioxx®, Merck). The final vote was 17 committee members in favor and 15 against.

"The data are very compelling," Wood said. "There is a clear signal that rofecoxib is substantially worse than other drugs. I don't think there's any reason to keep it on the market," he said. But other committee members argued in favor of marketing, based on the drug's indication as the only coxib available for juvenile rheumatoid arthritis (RA). Shafer noted that rofecoxib has demonstrated the strongest GI benefit, is available in once-daily dosing, and is the only coxib available for patients with allergies to sulfonamide.

During the discussion following the divided vote, the committees decided to implement stronger variations of the warnings they recommended for celecoxib. They also opted to dramatically reduce doses of rofecoxib. The committees recommended largely eliminating the 50-mg dose, favoring instead to cut the standard 25 mg dose to 12.5 mg.

While the group opted to maintain the product's indication for juvenile RA, members raised concerns. "I am worried about the potential silent and insidious effect this could have on children," said **Dr Gary Stuart Hoffman** (Cleveland Clinic Foundation, OH). Some panelists recommended allowing rofecoxib for children with parent informed consent and largely disallowing the product for adults except in specific compassionate-use circumstances.

Panelists react to lack of valdecoxib data

Recommendations for valdecoxib:

- Initiate stronger black-box warning than celecoxib.
- Halt direct-to-consumer advertising.
- Add educational materials.
- Contraindicate in cardiac surgery.

Committee members questioned whether valdecoxib (Bextra®, Pfizer) should have ever been approved at all, considering the "paucity of data" and the additional concern over adverse skin reactions. "It seems almost inconceivable to me that someone would prescribe this drug instead of celecoxib," Wood said. He added that with such a lack of data, there is no evidence that it is safer or more harmful.

Dr Curt Furberg (Wake Forest University, Winston-Salem, NC) said that in the absence of strong evidence, the committees need to reconsider whether valdecoxib should remain on the market. "Perhaps we have to face up to this and take it off the market," he said.

But in the end, the committees voted narrowly in favor of the overall risk-to-benefit profile supporting the continued marketing of valdecoxib. Seventeen members voted for and 13 against, and two abstained. "The panel clearly was concerned over the lack of long-term safety data and that was reflected in the unenthusiastic vote for retaining valdecoxib on the market," Shafer told **heart*wire*** in an interview following the meeting.

Members called for a strong black-box warning, educational materials such as a "Dear Healthcare Professional" letter and patient-education materials, no direct-to-consumer advertising, and a contraindication for cardiac surgery.

Combination therapy with aspirin and COX-2 selective agents ill advised, group says

Panelists discussed the role of the concomitant use of low-dose aspirin in reducing cardiovascular risk in patients treated with COX-2 inhibitors. While many members complained of a lack of data, the group as a whole voted against combination therapy. Many expressed concern that aspirin would offset the GI benefits of the selective agent and that physicians should therefore opt instead for a nonselective product.

"I've looked at all of the data and there's just no compelling evidence," said **Dr Steven Nissen** (Cleveland Clinic Cardiovascular Coordinating Center, OH).

The road to hell is paved with

"It goes both ways, and this is actually one of the biggest disappointments for the whole class, because when this hypothesis was raised, there were people who said, 'Don't worry about these drugs, just give everybody a baby aspirin everyday and you can reverse the toxicity of COX-2 inhibitors.' And it turns out that that hypothesis appears to be wrong — I've always said that the road to hell is paved with biological plausibility."

biological plausibility.

But, Nissen adds, the data on which to base this decision remain limited. "It would be useful, if this class of drugs were to survive in the long run, to study this in a more formal way with larger sample sizes."

Panel didn't stop at the coxibs; made recommendations for nonselective NSAIDs, too

The committees recognized that their proposals to the FDA would likely result in a market shift to other products such as nonselective NSAIDs or even selective products not currently marketed as coxibs, such as **meloxicam** (Mobic®, Boehringer Ingelheim). The group expressed concern that its decisions could instigate unintended consequences and it therefore opted to inform physicians and the public about concerns over other products as well. "We don't want people to switch to another drug and gain a false reassurance that there isn't a problem with that product, too," Nissen said.

The group decided that while warnings for all NSAIDs would be appropriate, it would be a mistake to issue identical blanket warnings and risk further confusing physicians and patients. "We need to attach appropriately graded warnings," Shafer argued.

The committees voted unanimously in favor of issuing black-box warnings for nonselective NSAIDs. And they opted for an individualized approach for each drug. In a press conference following the meeting, **John Jenkins**, the FDA's director of the Office of New Drugs, admitted that the committees' suggestion will be logistically complicated. "The more gradients there are in the recommendations, the more difficult it will be to do in a timely manner," he said.

Public reaction

"Even before the meeting was adjourned, the top story online in Yahoo was, 'Panel recommends pain drugs remain on the market,' " Shafer said. "This is correct, but it does not reflect the panel's very graded response to the risks of rofecoxib, the perceived relative safety of celecoxib compared with rofecoxib, and the concerns over the COX-2-selective NSAIDs, and reassuring data on naproxen." Shafer told **heart*wire***, "I'm afraid that the shades of gray that people heard during the meeting will be left out of the press announcement."