

FDA whistle-blower Graham blasts new Merck arthritis drug

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By Rita Rubin, USA TODAY

The arthritis drug that Merck has developed to compete with Celebrex may be as risky for the heart as Vioxx, writes Food and Drug Administration whistle-blower David Graham in an editorial posted online Tuesday by a medical journal.

In considering whether Arcoxia should be approved, "the FDA, academia, and the medical research enterprise are once again faced with the opportunity to forsake common sense by willfully accepting misdirection and disinformation presented in the guise of science," Graham writes on the *Journal of the American Medical Association's* website.

An editor's note says the FDA allowed Graham to write the editorial as a private citizen, not as an agency employee. The editorial and the two studies it accompanies will run in the Oct. 4 *JAMA*, but they were posted online early "because of the public health implications," a *JAMA* press release says.

Graham, a physician in the FDA's Office of Drug Safety, made news nearly two years ago when he told a Senate panel that the agency was "virtually defenseless" in preventing a "tragedy and profound regulatory failure" such as Vioxx.

Concerns for cardiovascular safety had spurred Merck to stop selling Vioxx in September 2004.

Like Vioxx and Celebrex, Arcoxia is a so-called COX-2 inhibitor. Their selling point has been a lower risk of bleeding stomach ulcers and other serious digestive tract complications than other non-steroidal anti-inflammatory drugs, or NSAIDs, such as ibuprofen.

A month after Vioxx was taken off the market, the FDA issued an "approvable letter" for Arcoxia, its successor, asking for more data on safety and effectiveness. The FDA still has not made a final decision on Arcoxia, which is sold in 62 countries.

In an August paper in the *American Heart Journal*, Merck scientists reported that preliminary analyses of clinical trial data showed that the rate of cardiovascular "events," such as heart attacks, was similar between Arcoxia and diclofenac, an older arthritis drug.

But one article posted online by *JAMA* raises serious questions about the cardiovascular safety of diclofenac, which, in turn, raise questions about the safety of Arcoxia. Researchers pooled the results of 23 studies in which people decided whether to take an NSAID. They found that diclofenac raised cardiovascular risk as much as lower-dose Vioxx. Only higher-dose Vioxx was riskier.

Co-author David Henry, a clinical pharmacologist at the University of Newcastle in Australia, says he has switched patients from diclofenac to naproxen, which, in his study and others, appears to be the only NSAID that doesn't raise cardiovascular risk. "It causes gastrointestinal bleeding, no question," he says. "But I'd rather have a gastrointestinal bleed than a heart attack."

For that reason, says Wake Forest University medical epidemiologist Curt Furberg, the FDA should pull diclofenac off the market and remove the "black box" warning about cardiovascular risk, which the FDA ordered on all NSAIDs in April 2005, from naproxen's label.

"The take-home message is stay away from diclofenac, which is basically another way of saying that Arcoxia is harmful," says Furberg, who sits on the FDA's Drug Safety and Risk Management Advisory Committee.

In a statement, Merck said the results of the Arcoxia/diclofenac comparison "are consistent with FDA's April 2005 memo stating that long-term clinical trials have not shown a difference in cardiovascular safety" between COX-2s and other NSAIDs, "with naproxen as a possible exception."

A second paper on *JAMA's* website pooled the results of 114 clinical trials in which volunteers were randomly assigned to take a COX-2 inhibitor or another NSAID or a placebo. Only Vioxx was found to raise the risk of heart rhythm abnormalities and kidney-related problems.

Co-author Eric Ding, a doctoral candidate at the Harvard School of Public Health, cautions that the finding does not necessarily mean Arcoxia and Celebrex are safe.

"I just want to say that in the (COX-2) class analysis, Vioxx seemed to stand out," Ding says.