

Timeline of Pain Reliever Controversy

Tracing the Path on Cox-2, NSAID Pain Relievers

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April 7, 2005 -- Today's news that the [arthritis drug Bextra has been withdrawn from the market](#) is the latest in a series of headlines about two types of pain relievers: Cox-2 inhibitors (Bextra, Celebrex, and Vioxx) and traditional nonsteroidal anti-inflammatory drugs (NSAIDs).

Here's a look at the course of events:

- **Sept. 30, 2004** -- The pain reliever Vioxx is voluntarily withdrawn from markets worldwide by the drug's maker, Merck & Co. The decision follows news from a large clinical trial in which long-term use of the drug (18 months or more) doubled participants' risk of heart attack and stroke. Calling the risk "small" to any particular patient, the FDA says, "We think Merck is doing the right thing."

Since Vioxx is a Cox-2 inhibitor drug, some people wonder if other drugs in the same class (namely, Celebrex and Bextra) might have similar risks.

- **Dec. 9, 2004** - The FDA orders a new, bold-faced warning on Bextra labels, cautioning that the drug should not be taken by patients undergoing heart bypass surgery. The FDA also strengthens warnings about the risk of serious, potentially fatal skin reactions to Bextra.
- **Dec. 17, 2004** -- A cancer-prevention study shows that Celebrex more than doubled heart deaths, heart attacks, and strokes in people enrolled. The National Cancer Institute stops the study. However, the affected participants were taking twice the normal amount of Celebrex usually prescribed for arthritis.

Also, *The New England Journal of Medicine* publishes a letter by Vanderbilt University researcher Wayne A. Ray, PhD, and colleagues questioning Bextra's safety.

- **Dec. 23, 2004** -- The FDA issues a public health advisory about nonsteroidal anti-inflammatory drugs (NSAIDs) including Cox-2 inhibitors.

The advisory says that "recently released data from controlled clinical trials showing that the Cox-2 selective agents (Vioxx, Celebrex, and Bextra) may be associated with an increased risk of serious cardiovascular events (heart attack and stroke), especially when they are used for long periods of time or in very high-risk settings (immediately after heart surgery)."

The advisory also says that long-term use of another NSAID, naproxen (sold as Aleve, Naprosyn, and other trade or generic names) "may also be associated with an increased cardiovascular risk, compared to placebo."

The National Institutes of Health had suspended the study that showed that risk with naproxen. Later, the researchers said reports of naproxen's heart effects were overblown and unnecessarily scared the public (see Feb. 18, 2005).

- **Jan. 18, 2005** -- Two new studies suggest that combining Bextra with aspirin may increase the risk of blood clots that could trigger a heart attack or stroke.
- **Jan. 24, 2005** - A study in the *Archives of Internal Medicine* says Celebrex and Vioxx have been widely overused.
- **Jan. 31, 2005** -- Health insurance company Kaiser Permanente says it will no longer offer Bextra, citing concerns that the drug's potential benefits were not worth the potential risks.
- **Feb. 16, 2005** -- The FDA opens a federal inquiry into Cox-2 inhibitors.

On the same day, Merck presents data suggesting that heart risks with Vioxx do not show up until patients have taken the drug for at least 18 months.

- **Feb. 17, 2005** -- A previously undisclosed study presented by an FDA safety officer says the most common dose of Celebrex (200 milligrams per day) does not increase heart attack risk. "Above 200 milligrams, we believe there is evidence of increased risk," FDA whistleblower David Graham, MD, says. Pfizer, which markets Celebrex, says most studies did not show an increased heart risk with their drug and that safety concerns appear to be unique to Vioxx.

Graham also says an analysis suggests that Vioxx may cause heart attacks much earlier than the 18 months mentioned in Merck's presentation a day earlier.

Several experts tell the FDA's advisory panel there's enough evidence to suggest that Vioxx, Bextra, and Celebrex all raise the risk of heart attack and stroke.

- **Feb. 18, 2005** -- An FDA advisory panel says the arthritis drug Vioxx can return to the market and that Celebrex and Bextra should remain available -- with strict warnings that Cox-2 inhibitors can raise the risk of heart attack and stroke.

The panel also recommends that labels for many of the more than 20 older anti-inflammatory drugs be updated to warn consumers and doctors that they may carry a heart risk. Three of those drugs -- ibuprofen, naproxen, and ketoprofen -- are available over the counter.

The expert recommendations to go the FDA, which is not obligated to follow them but generally does.

Also, Johns Hopkins University researcher Constantine Lyketsos, MD, tells the panel that reports about naproxen (Aleve, Naprosyn, etc.) and heart attack are overblown. Lyketsos, who worked on the study, says the drug's heart effects were "barely significant." He says some participants became hesitant to take their drugs in the wake of concerns about Vioxx and other drugs.

- **April 7, 2005** --The drug company Pfizer suspends sales of Bextra after the FDA asks it to pull the drug off the market. Pfizer says it disagrees with the FDA's request and hopes to reintroduce the drug later.

The FDA also asks Pfizer to include a boxed warning on the Celebrex label; Pfizer agrees to work with the agency. The warning highlights the potential risk of heart attack and stroke with Celebrex as well as the potential for serious, life-threatening stomach ulcer bleeding.

In addition, the FDA asks makers of all NSAIDs to revise their labels to include more specific information on potential heart and stomach ulcer bleeding risks. The FDA also wants those drugs' labels to provide information to help consumers use those drugs safely.

Makers of over-the-counter anti-inflammatory drugs are also asked by the FDA to include a warning about potential heart and stomach ulcer bleeding risks.

SOURCES: WebMD Medical News: "Arthritis Drug Vioxx Pulled Off Market." FDA Talk Paper, "Bextra Label Updates with Boxed Warning Concerning Severe Skin Reactions and Warning Regarding Cardiovascular Risk," Dec. 9, 2004. FDA Talk Paper, "FDA Issues Public Health Advisory Recommending Limited Use of Cox-2 Inhibitors." WebMD Medical News: "Jury Still Out On Celebrex Safety." WebMD Medical News: "Study: Low-Dose Celebrex Poses No Heart Risk." WebMD Medical News: "More Evidence of Heart Risks from Bextra." WebMD Medical News: "Vioxx, Celebrex Were Overused." WebMD Medical News: "FDA Panel Members: All Arthritis Drugs Suspect." WebMD Medical News: "Despite Risks, Pain Relievers Given OK."

WebMD Medical News: "Naproxen Warning Unjustified, Say FDA Experts." WebMD Medical News: "Bextra Taken Off Market; Celebrex Gets Warning."

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