

DRUG REGULATION

Rofecoxib (Vioxx) voluntarily withdrawn from market

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Merck & Co. announced Sept. 30 a voluntary worldwide withdrawal of rofecoxib (Vioxx) after a study showed patients taking the drug on a long-term basis face twice the risk of a heart attack compared with patients receiving placebo.

The 3-year clinical trial called APPROVe (Adenomatous Polyp Prevention of Vioxx), which was halted in late September (2 months before it was scheduled to end), was evaluating the efficacy of rofecoxib in preventing the recurrence of colorectal polyps among patients with a history of colorectal adenomas. It revealed an increased relative risk for serious cardiovascular events, including heart attacks and strokes, beginning after 18 months of treatment among patients taking rofecoxib that was about twice that of patients taking placebo. The results for the first 18 months of the study did not show any increased risk.

The randomized, placebo-controlled, double-blind study enrolled 2600 patients at 100 sites. According to Merck Frosst Canada, when the study was halted 25 of those taking placebo had suffered a cardiovascular event, and 45 of those taking rofecoxib had suffered an event (relative risk 1.8). The absolute risk difference is about 1.5% over the period of the study.

No one died, said Dr. François Bertrand, executive director of medical research for Merck Frosst Canada. The study's external safety monitoring

board recommended that the trial be halted, but "because of the nature of the events and the availability of other drugs, we decided the right thing was to discontinue [the drug]," said Bertrand.

The risk of a patient having a cardiovascular event related to rofecoxib is "very small," stated Acting US Food and Drug Administration (FDA) Commissioner Dr. Lester M. Crawford, but "overall, patients taking the drug chronically face twice the risk of a heart attack compared to patients receiving a placebo." Crawford said the FDA will closely monitor other drugs in this class for similar side effects.

Rofecoxib, a selective COX-2 inhibitor, nonsteroidal anti-inflammatory drug (NSAID) gained Canadian approval in 1999. It is currently approved for the treatment of acute and chronic symptoms of osteoarthritis, rheumatoid arthritis, acute pain and menstrual pain.

At the time of approval, the company's trials indicated there was not an increased risk of cardiovascular events with rofecoxib compared with placebo or other NSAIDs.

However, the Vioxx Gastrointestinal Outcomes Research (VIGOR) study, released in March 2000, did indicate an increased risk compared with naproxen. Health Canada issued an advisory in 2002 about increased risk of cardiovascular events related to the drug's use. Since then Health Canada has been moni-



Merck Sharp & Dohme (Asia) Ltd.

Rofecoxib was available and promoted in 80 countries, including China.

toring all COX-2 inhibitors for gastrointestinal and cardiovascular events. (See also *CMAJ* 2002;166[12]:1692-3.)

The lead author of the VIGOR study, Dr. Claire Bombardier, said withdrawing the drug was "pretty honourable and gutsy of [Merck]." She was part of an advisory group to the company in September; many members recommended the drug not be withdrawn because patients need various drug options.

"They are withdrawing a drug that was very effective," said Bombardier, director of rheumatology at the University of Toronto.

The puzzling thing, she adds, is why the increased risk didn't show up until after 18 months. The question that remains is

whether the increased risk applies only to rofecoxib or to all COX-2 inhibitors. "I really think the regulatory agencies should ask all COX-2 manufacturers to do this kind of study."

Dr. James Wright, a professor of pharmacology at the University of British Columbia, has long maintained (*CMAJ* 2002;167[10]:1131-7) that continued licensing of this class of drug "should be dependent on demonstrating they are safe."

He advocates for RCTs comparing these drugs to a nonselective NSAID, such as ibuprofen. "We should have started this a long time ago."

COX-2 inhibitors block 1 enzyme, which Wright says strikes an imbalance in the bleeding/clotting action toward clotting. "Rofecoxib is more potent so it emerged as the worse, but the same property would apply to all COX-2 inhibitors."

Rofecoxib, which is available in more than 80 countries, had worldwide sales of \$2.5 billion in 2003. IMS Health Canada reports that rofecoxib was the number 10 top-selling drug in Canada in 2003, with 3.3 million prescriptions written and retail sales totalling \$194 million.

"The fact that so many are prescribed is unfortunate," says

Wright. "Doctors should be cautious about any of these drugs."

Health Canada has posted an advisory about the drug's withdrawal (www.hc-sc.gc.ca). Spokesperson Jirina Vik said rofecoxib will be withdrawn at wholesalers, pharmacies and physicians' offices.

Health Canada advises patients taking rofecoxib to contact their physician about alternative treatments and to return any leftover rofecoxib to their pharmacy for a refund.

For more details, physicians can contact Merck at 888 368-4699 or at www.merck.com. — *Barbara Sibbald, CMAJ*

ABORIGINAL HEALTH

Lack of Aboriginal health professionals a "huge issue"

The federal government's announcement of \$100-million over 5 years to train Aboriginal health professionals is welcome news, but unlikely to make a big dent in the shortfall, medical insiders say.

"It sounds like a lot of money, but in fact it's not going to be that much once you do this and that over 5 years, and it's such a huge issue to deal with," said Malcolm King, a principal investigator at the University of Alberta's Aboriginal Health Research Training Program.

In 1996, the Royal Commission on Aboriginal Peoples (RCAP) concluded that Canada needed another 10 000 Aboriginal health professionals — a 10-fold increase.

An estimated 150 physicians

of Aboriginal heritage now practise in Canada, a modest increase over the past decade according to Bernice Downey, executive director of the National Aboriginal Health Organization. "We know it has increased over the years, but we need to do more work," said Downey.

Health Canada has not announced how the \$100-million funding for the Aboriginal Health Human Resources Initiative will be spent, except to say it aims to increase recruitment and retention and change curricula so that health professionals "are better equipped to address the cultural differences."

"Everyone will be looking anxiously as to how that pot of money will unfold," said Downey. She hopes the money will augment existing programs to boost enrolment. Much of that work, she said, begins long before college. For instance, children in remote and Aboriginal communities need greater exposure to math and science in their curriculum, and more encouragement from parents and teachers to choose nontraditional careers like medicine.

In 1988, the University of Alberta began a concerted effort to train Aboriginal doctors. To date there are 33 graduates and

another 20 students enrolled in the 4-year program.

"There are other programs in the country, but we have certainly graduated the largest number in the shortest time frame," said Anne-Marie Hodes, coordinator of the university's Aboriginal Health Care Careers Program.

But 4 or 5 new graduates a year isn't sufficient to fill the gap, says King. "We need all the medical schools in the country to be more active in programs to recruit and train Aboriginal health professionals."

In Ontario, for instance, there are only 12 practising Aboriginal doctors and 16 medical students enrolled at five medical schools. The province needs at least 375 physicians, a September health conference at Six Nations in Oshweken, Ont., was told. Chief Roberta Jamieson will chair a committee of key health care players to develop a pre-med program for Aboriginal students at Ontario universities, including pre-admission and in-school support, and to devise ways to recruit more qualified students.

The \$100 million from Ottawa is part of a \$700-million commitment to Aboriginal health Prime Minister Paul Martin announced Sept. 13. — *Amy Jo Elman, Saskatoon*

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Critical shortage: Only about 150 physicians of Aboriginal heritage practise in Canada.

Canapress, R. Galbraith