## Ibuprofen should go behind-the-counter says expert panel

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A Health Canada expert advisory panel says ibuprofen should go behind-the-counter at pharmacies due to new evidence showing that at prolonged high doses its risk of cardiovascular incident is comparable to prescription COX-2 drugs, such as rofecoxib (Vioxx).

But Health Canada has rejected the advice of its panel, arguing that the evidence to support such a move is lacking.

Ibuprofen is the only traditional non-steroidal anti-inflammatory drug (NSAID) available over-the-counter in Canada (others, such as naproxen and diclofenac, are by prescription only). Putting ibuprofen behind-the-counter would allow pharmacists to warn consumers of this potential adverse effect.

In its final report, Health Canada's Expert Advisory Panel on the Safety of COX-2 Selective Non-steroidal Anti-Inflammatory Drugs acknowledged that while over-the-counter ibuprofen is intended for short-term use only, in reality, the drug is "frequently being used chronically and at a high dose." the June 2005 report states that "Health Canada should consider that ibuprofen only be sold after discussion with a pharmacist...."

But Health Canada took issue with that recommendation and conducted its own scientific review, which was released June 14. It concluded that the cardiovascular safety of ibuprofen sold over-the-counter is not well documented, but is "considered satisfactory," says Dr. Marc Berthiaume, director of Marketing Pharmaceuticals and Medical Devices Bureau.

He says there's a need for long-term randomized controlled trials to demonstrate the validity of safety concerns.

The decision about whether ibuprofen should go behind-the-counter now rests with National Association of Pharmacy Regulatory Authorities. "The place of sale for a drug, once it is removed from Schedule F, is determined by provincial and territorial pharmacy regulatory authorities," stated Health Canada spokesperson Christopher Williams.


Canapress

Health Canada says the safety of ibuprofen is "considered satisfactory" but its expert advisory panel disagrees, and advises putting it behind-the-counter at pharmacies.

Health Canada sent a letter to NAPRA a year ago advising it of the expert advisory panel's recommendations. NAPRA referred the matter to its National Drug Scheduling Advisory Committee. In correspondence with *CMAJ*, NAPRA President Janet Bradshaw stated that they told Health Canada in February that ibuprofen's retail sales status would not be reviewed "due to the lack of evidence from the [Health Canada expert advisory panel] that this would be in the public interest."

She further states: "Health Canada apparently did not uncover any scientific evidence to support the suggestion from the [expert advisory panel] that ibuprofen be moved from retail shelves to behind-the-counter status of pharmacies."

However, Dr. Andreas Laupacis, who headed Health Canada's expert advisory panel on the COX-2 drugs, disagrees, saying there is enough evidence to support a move. "We should treat coxib and noncoxib NSAIDs the same way. We felt it would be reasonable to have [ibuprofen] behind-the-counter."

The panel's recommendation is borne out by a June 2006 meta-analysis of 138 randomized trials involving 144 296 patients (*BMJ* 2006;332:1302-8). Evidence from an earlier version of this study was included in the expert advisory panel's report. The *BMJ* study concluded that "overall, the incidence of serious vascular events was similar between a selective COX-2 inhibitor and any traditional NSAID."

The rate of adverse event is 1.0% per year for COX-2 inhibitors v. 0.9% per year for traditional NSAIDs (95% confidence interval). The rate ratio is 1.16 for COX-2 inhibitors v. 0.69 to 1.12 traditional NSAIDs. (Naproxen is an exception to this finding.)

"Clinically, people have known this for years," says Laupacis, the president and CEO of the Institute for Clinical

Evaluative Sciences. "It's not infrequent to admit people [to hospital] for heart failure after they've taken NSAIDs."

At low doses for a week or so, traditional NSAIDs are "not worth fussing about," he added. "But if people are using chronically, it might be a decent thing to know [about potential adverse events]."

Although the evidence of potential adverse events wasn't deemed sufficient to move ibuprofen behind-the counter, safety concerns were sufficient to persuade Health Canada to include new warnings in all traditional NSAIDs, including ibuprofen.

"We found an increase in relative risk [of cardiovascular events with prolonged use and high dosage] of NSAIDs compared to placebo and this wasn't known before and needed to be integrated into the labels," says Berthiaume. High dosage is defined as the highest approved dosage; the time period was not defined, but all the studies reviewed ran for more than 3 months.

Berthiaume couldn't say when the new labels will appear, adding that it depends on financial resources and "competing priorities" at Health Canada. "There's a relatively good level of awareness [of the risk of serious cardiovascular events] among health care professionals, and hopefully among the public," he added.

The US Food and Drug Administration told drug manufacturers to beef up warnings on nonprescription NSAIDs by Dec. 15, 2005.

The evidence of potential vascular and cardiovascular risks arose from some COX-2 inhibitor studies that used NSAIDs as comparators, thus generating data on those drugs' risks.

Health Canada launched a review of the cardiovascular risks associated with COX-2-selective NSAIDs, including rofecoxib, valdecoxib (Bextra), celecoxib (Celebrex) and meloxicam (Mobicox and other generics), after Merck & Co. withdrew rofecoxib from the world market on Sept. 30, 2004 due to new findings regarding its cardiac risk (see story on page 234). — Barbara Sibbald, *CMAJ*

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## Vioxx should be allowed back on the market advises expert panel

Rofecoxib (Vioxx) ought to be allowed back on the market, concludes Health Canada's Expert Advisory Panel on the Safety of COX-2 Selective Non-steroidal Anti-Inflammatory Drugs (NSAIDs).

After Merck & Co. withdrew rofecoxib from the world marketplace on Sept. 30, 2004 (*CMAJ* 2004;171[9]: 1027-8), Health Canada launched a review of the cardiovascular (CV) risks associated with COX-2-selective NSAIDs, including rofecoxib, valdecoxib (Bextra), celecoxib (Celebrex) and meloxicam (Mobicox and other generics). The 400-page review includes pre-clinical and clinical trials, adverse drug reaction reports and other data.

In its comments on that review, released in June 2006, Health Canada decided that both rofecoxib and valdecoxib (which was withdrawn in December 2005 following evidence of increase CV events and severe cutaneous adverse reactions) will remain off the market unless a new drug submission is received and approved by Health Canada.

"At this time, we have not made a decision about whether to resubmit," says Merck Frosst spokesperson Marlene Gauthier.

The 13 members of the Expert Advisory Panel, who met for 2 days in Ottawa in June 2005, included people with backgrounds in rheumatology, cardiology, gastroenterology, internal medicine, family medicine, clinical trial methodology and epidemiology, plus 2 patients with rheumatoid arthritis. The report was released in July 2005.

The panel voted 12 to 1 in favour of potential future sales for rofecoxib, noting that most NSAIDs carry cardiovascular risk and that rofecoxib has a decreased frequency of both gastrointestinal intolerance and peptic ulcer diseases compared with traditional non-selective NSAIDs, and that "patients benefit from having a variety of drugs to choose from." The panel did not recommend that valdeocoxib go back on the market due to the rare but severe skin reactions.

"There's no question [rofecoxib] increases cardiovascular risk compared to placebo," says Dr. Andreas Laupacis, who headed Health Canada's Expert Advisory Panel. "But the absolute increase is very small."

Given that the risk is comparable to that of traditional NSAIDs, such as ibuprofen (see article on page 233), but that it has a lower incidence of gastrointestinal problems, "What's the rationale for not making it available?" asked Laupacis the president and CEO of the Institute for Clinical Evaluative Sciences.

> "Patients benefit from having a variety of drugs to choose from."

Health Canada's comments on that review and own scientific review of certain COX-2s, recommend shorter and lower doses of all COX-2s and traditional NSAIDs.

"That's clear in the report," says Dr. Marc Berthiaume, director of Marketing Pharmaceuticals and Medical Devices Bureau.

During public consultations, Berthiaume says people indicated they wanted to know the risk, but they also wanted to be able to "make that choice."

Health Canada's review concludes that the "benefit–risk balance favours" the continued sale of celecoxib and meloxicam. In accordance with the panel's recommendations, the labels were revised in September 2005 to warn of the increased risk of CV adverse events and to suggest using these drugs at the "lowest effective dose for the shortest possible duration of treatment."