

**SUMMARY:**  
**Report of the Expert Advisory Panel on the Safety of Cox-2 Selective  
Non-steroidal Anti-Inflammatory Drugs (NSAIDs)**

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## **Background**

Cox-2 selective inhibitors are used to relieve pain resulting from a variety of musculoskeletal disorders. Numerous studies have shown that their effectiveness in pain relief is similar to "traditional" nonsteroidal anti-inflammatory drugs (NSAIDs), although some patients seem to respond preferentially to one drug and not another. Cox-2 selective inhibitors were first marketed in Canada in 1999 as anti-inflammatory medications that have less gastrointestinal side-effects (e.g. ulcers) than "traditional" NSAIDs. As a result of this benefit, and aggressive marketing, Cox-2 selective inhibitors have become one of the most commonly prescribed drugs in Canada.

In 2004, Merck voluntarily withdrew Vioxx from the market due to concerns that the drug increases the risk of cardiovascular disease (e.g. heart attacks and strokes), and Pfizer suspended sales of Bextra due to concerns about a rare but serious skin disorder and short-term cardiovascular risk. At the present time, Celebrex is the only Cox-2 selective inhibitor available in Canada.

## **The Expert Advisory Panel: Its Deliberations and Findings**

To examine the safety of Cox-2 inhibitors (Vioxx, Bextra and Celebrex), Health Canada convened an arm's length expert advisory panel. The panel consisted of 13 individuals with backgrounds in rheumatology, cardiology, gastroenterology, internal medicine, family medicine, clinical trial methodology, and epidemiology. Two members of the panel were individuals with rheumatoid arthritis.

Through its deliberations, the Panel addressed the following questions and arrived at the conclusions identified below.

**1) *Do Cox-2 selective inhibitors significantly increase the risk of cardiovascular events such as heart attack and stroke?***

Yes, compared with a placebo, the use of Cox-2 selective inhibitors does increase the risk of cardiovascular events, although the absolute risk is greater when these drugs are taken for longer periods of time, when patients have a history of or risk factors for heart disease, and perhaps, as dosage increases. However, the increased risk of cardiovascular disease caused by Cox-2 selective inhibitors seems similar to the increased risk associated with most NSAIDs.

**2) *Is the use of aspirin helpful in reducing the cardiovascular risk in patients treated with Cox-2 selective inhibitors?***

There was no convincing data to show that the addition of aspirin to Cox-2 selective inhibitors protects against the increased risk of cardiovascular disease, and worrisome data suggesting that aspirin attenuates or negates the gastrointestinal "protective" effect of selective Cox-2 selective inhibitors. However, a systematic review of the effect of the addition of aspirin to a Cox-2 selective inhibitor upon cardiovascular and gastrointestinal events has not been undertaken.

**3) *Do the overall benefits and risks of Cox-2 selective inhibitors justify the marketing of these drugs in Canada?***

Based on available information on each drug, the Panel voted:

- i. Unanimously that Celebrex continue to be marketed in Canada, because a) the increased risk of cardiovascular disease caused by Celebrex appears similar to that of most NSAIDs, b) the risk of

gastrointestinal harm caused by Celebrex appears less than most NSAIDs, and c) patients benefit from having a variety of drugs to choose from for pain relief.

ii. 12 to one that Vioxx be allowed back on the market, with the rationale for the majority position being similar to that of Celebrex. The one vote against the reintroduction of Vioxx was based on the panel member's feeling that the evidence suggested that Vioxx caused a greater increased risk of cardiovascular harm than Celebrex (especially at higher doses) and that this risk was sufficiently high to justify continuing not to market Vioxx, especially since alternatives are available.

iii. Eight to five that Bextra NOT be allowed back on the market. The majority: a) felt that there was not sufficient information available about the cardiovascular risk associated with Bextra, b) was concerned with the possible increase in a rare but serious skin disorder, and c) felt that numerous other NSAIDs with more complete information about benefits and harms are already on the market. The minority who voted that Bextra should be marketed felt that a) the increased risk of cardiovascular disease caused by Bextra is likely to be similar to that of other Cox-2 selective inhibitors, b) the number of patients suffering severe adverse skin reactions is very small and similar to many other drugs still on the market, and c) some patients will benefit from having another anti-inflammatory agent available. Those who voted for the marketing of Bextra felt that it should only be marketed as a third-line anti-inflammatory agent to be used if others have failed.

**4) *Are there patient populations in which the potential risks of Cox-2 selective inhibitors outweigh the potential benefits?***

Yes. While these drugs can be quite beneficial for some patients, for others their use can come with considerable risk (e.g. for patients that have just had open heart surgery). The appropriate use of Cox-2 selective inhibitors should be influenced by the individual circumstance of each patient.

**5) *What actions does the Panel recommend that Health Canada consider implementing to ensure the most appropriate use of these medications?***

These comments relate to Celebrex and Vioxx only, since Bextra was not recommended for use in Canada. The Panel felt that:

- Warnings about the risks of Cox-2 selective inhibitors should be added to product monographs and material given to patients;
- Evidence-based consumer summaries should be disseminated to consumers;
- Pharmaceutical advertising should prominently identify the increased risk of hypertension, edema, kidney disease and cardiovascular events; and
- Guidelines for physicians and pharmacists should be developed and disseminated, describing the benefits and risks of Cox-2 selective inhibitors and NSAIDs, as well as the indications for their use.

**6) *What additional studies are essential to further evaluate the potential cardiovascular risk of all NSAIDs (conventional and Cox-2 selective inhibitors)?***

A number of future studies were recommended ranging from systematic reviews, to large randomized trials, to post-marketing evaluations to assess outcomes in the 'real world' and rare side-effects of the drugs.

The panel strongly recommends that when a drug is being considered for marketing by Health Canada, pharmaceutical manufacturers must publicly release **all** data (published and unpublished) from completed randomized trials and other studies of relevance to the safety and efficacy of their drugs. They should also register all ongoing trials publicly. As well, Canadian regulations should be modified to ensure that all material submitted to Health Canada in support of a request to license a drug (as well as Health Canada's assessment of that drug) is made publicly available. This information on Cox-2 selective inhibitors should be made available immediately.