Translated from ***Rev Prescrire*** **July-August 2005 ; 25 (263): 512-513**

CELECOXIB STILL ON THE MARKET: BUT FOR WHOSE BENEFIT?

● **The cardiovascular risks associated with Cox-2 inhibitor therapy were confirmed in early 2005, and measures restricting the use of these drugs were taken in several countries. Yet celecoxib remains on the market.**

● **Comparative trials versus other NSAIDs failed to show that celecoxib was any more effective for pain relief. And, following damning revelations that the CLASS study results had been manipulated, it became clear that celecoxib had no tangible advantage in terms of serious gastrointestinal complications.**

● **An increase in Cox-2 inhibitor prescriptions, primarily based on their reputation for better tolerability, led to an increase in the absolute number of cases of gastrointestinal haemorrhage.**

● **A trial focusing on the prevention of colorectal polyps showed that cardiovascular events occurred two to three times more frequently with celecoxib than with placebo. Another trial showed no significant difference.**

● **In a trial involving patients with Alzheimer's disease, overall mortality was higher with celecoxib than in the placebo group. The difference was similar to that observed in placebo-controlled trials of rofecoxib in Alzheimer's disease.**

● **The celecoxib affair once again highlights certain failings of the American and European regulatory agencies: celecoxib is still on the market, exposing patients to risks associated with its use without providing any therapeutic advantage.**

The Cox-2 inhibitor affair is far from over. The cardiovascular risks associated with these drugs have been confirmed, and various restrictions on their use have been imposed in several countries, including simple market withdrawal, restricted use, and changes in the summaries of product characteristics (SPC).

Market withdrawal of several Cox-2 inhibitors. Rofecoxib was withdrawn globally in September 2004 because of an increase in cardiovascular adverse effects, including an increase in overall mortality in several trials involving patients with Alzheimer's disease (3.8% versus 2.14% on placebo, $p<0.03$). Overall mortality was already higher with rofecoxib than with naproxen in the earlier VIGOR trial (1,2).

Valdecoxib was withdrawn from the market in the United States and then in Europe, in April 2005, due to serious cardiovascular and cutaneous adverse effects (3). Among the reasons cited for market withdrawal, the US Food and Drug Administration (FDA) explicitly took into account the absence of any therapeutic advantage over other nonsteroidal antiinflammatory drugs (NSAID) (4).

Parecoxib was withdrawn from the Swiss market in May 2005.

In Europe, all Cox-2 inhibitors were contraindicated in patients with ischaemic heart disease and stroke in early 2005. Etoricoxib, marketed in several European countries (but not in France), was also contraindicated in patients with uncontrolled hypertension, due to the risk of cardiovascular events (5).

Celecoxib is still on the market in several countries, including France and the United States.

No better pain relief, but serious gastrointestinal adverse effects. Celecoxib has not been shown to be any more effective than other NSAIDs for pain relief (6). Yet Cox-2 inhibitor campaigns claimed that these drugs were "*as effective as conventional antiinflammatory drugs but have far better gastric tolerability*" (7). These claims were essentially based on the results of the CLASS trial published in 2000.

Data manipulation. Damning revelations that the CLASS results were "massaged", and a re-analysis of the data, have since shown that celecoxib has no tangible advantage with respect to serious gastrointestinal complications (8).

In April 2004, the European Medicines Agency (EMEA) re-evaluated the Cox-2 inhibitors and concluded that "*available data indicated that significant and consistent gastrointestinal benefit of Cox-2 inhibitors compared with conventional NSAIDs has not been demonstrated*" (9).

No new data have emerged since then to challenge this evaluation of celecoxib.

Unjustified exposure of at-risk patients. A Canadian team conducted a publicly funded analysis of a database containing information on 1.3 million Ontario inhabitants aged over 65 years. They found that, after the market release of rofecoxib and celecoxib, the number of new NSAID users rose by 90 000 per year, and that this increase corresponded to the number of initial Cox-2 inhibitor prescriptions. The number of hospital admissions for gastrointestinal haemorrhage then rose by 650 cases per year (10).

Thus, an increase in NSAID prescriptions in Ontario, based on the better reputation for safety of Cox-2 inhibitors, in fact led to an absolute increase in the number of cases of gastrointestinal haemorrhage.

Increased cardiovascular risks. The Cox-2 selectivity of Cox-2 inhibitors raised the possibility of a higher thrombotic risk: the resulting lack of antiplatelet effect might tilt the prostacyclin/thromboxane balance towards thromboxane, which tends to promote platelet aggregation (11). ►►

▶ An FDA analysis of the CLASS trial results showed an increase in angina (stable and unstable) in patients treated with celecoxib who were also using aspirin, although the difference was not statistically significant (4.1% with celecoxib, 2.9% with ibuprofen) (10).

Confirmed risk of thrombosis and heart failure. A placebo-controlled trial of celecoxib in the prevention of colorectal polyps (the APC study), funded by the American National Cancer Institute and Pfizer, showed that the risk of cardiovascular events rose by a factor of 2 to 3 after about three years of celecoxib therapy. This corresponded to an increase of about 5 to 8 events per 1000 patient-years of celecoxib treatment, based on a composite endpoint combining cardiovascular death, myocardial infarction and stroke (12,13). The risk was dose-dependent, with a relative risk of 2.5 with celecoxib 400 mg/day and 3.4 with 800 mg/day (13).

Rofecoxib was withdrawn from the market in 2004, when a trial with a similar protocol to the APC study showed an increase of about 7.5 cardiovascular events per 1000 patient-years of rofecoxib therapy versus placebo, the same level of risk observed with celecoxib (12).

Another similar trial (PreSAP), conducted by Pfizer and focusing on colonic polyposis, showed no significant difference between celecoxib 400 mg/day and placebo, based on the same composite endpoint combining cardiovascular death, myocardial infarction and stroke, after three years (about 18 cases per 1000 patient-years) (13,14).

Mortality: few but troubling data. The Adapt trial involving patients with Alzheimer's disease compared celecoxib 400 mg/day with naproxen and placebo (14). The trial was terminated prematurely, when an interim analysis of 750 patients treated for more than 18 months showed that both NSAIDs, especially naproxen, caused an excess of adverse effects. In another placebo-controlled trial of celecoxib, in which 425 patients with Alzheimer's disease were treated for about one year, the overall mortality rate was higher in the celecoxib group, with 13 deaths due to various causes in the celecoxib group (4.6%), versus 4 deaths (2.9%) in the placebo group (14).

The overall mortality rate in trials of rofecoxib in Alzheimer's disease was 3.8% (2.1% with placebo; $p<0.03$) among a total of more than 2000 patients treated for about 20 months on average (15). The overall mortality rate in the trial of celecoxib described above was comparable to that observed in trials of rofecoxib. The difference was not significant in the celecoxib trial, but only 425 patients were enrolled.

In April 2005 the FDA requested a long-term trial comparing celecoxib with naproxen (4).

Serious cutaneous events, plus the other adverse effects of NSAIDs. Cases of anaphylactic shock and Lyell's syndrome have been reported with celecoxib. In June 2004, EMEA issued reinforced warnings on the risk of hypersensitivity and severe cutaneous reactions to Cox-2 inhibitors, including exfoliative dermatitis, Stevens-Johnson syndrome, Lyell's syndrome, anaphylaxis, and Quincke's reaction (9). Allergic cross-reactions between sulphonamides and celecoxib may be a risk factor in some cases (9,16,17).

Celecoxib also exhibits the other adverse effects associated with NSAIDs, particularly the risk of renal failure (17).

Agency failings. The celecoxib affair illustrates the inadequacies of European and American regulatory agencies, which failed to identify, or to act upon, the weaknesses of the initial pre-market data, as well as repeated warning signs that arose during postmarketing surveillance.

On 23 June 2005, EMEA concluded that "*the balance of benefits and risks remains positive for these Cox-2 inhibitors used in their target patient populations*" (18). A new contraindication has been added concerning peripheral arterial disease. As of 21 July 2005, EMEA had not made available the data supporting its conclusions.

The US Food and Drug Administration (FDA) published its own re-evaluation, However, it has since emerged that no fewer than one-third of the members of the commissions that assessed the Cox-2 inhibitors in early 2005 had conflicts of interest with the drug companies concerned and, crucially, that these members voted differently from their peers (2).

Financial interests first. The risks associated with Cox-2 inhibitors can no longer be ignored. EMEA concluded in April 2005 that "*the increased risk of cardiovascular adverse effects is a class effect of Cox-2 inhibitors*" and, in April 2004, that "*available data show no significant and consistent gastrointestinal advantage of Cox-2 inhibitors compared with conventional NSAIDs*" (2,9).

Celecoxib remains on the market. This means that patients continue to be exposed to the risks of a drug that offers no therapeutic advantage.

In practice: don't use celecoxib. In summary, celecoxib is no more effective and has no tangible advantages in terms of gastrointestinal safety in comparison with traditional NSAIDs. In contrast, it carries a higher risk of serious cardiovascular and cutaneous adverse effects that have not yet been precisely quantified.

In practice, there is no reason to expose patients to this additional risk. When NSAID therapy is needed, it is best to use a standard NSAID such as ibuprofen or diclofenac, at the lowest effective dose and for the shortest possible time.

Selected references from Prescrire's literature watch.

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