Going against the flow: the impact of PHARMAC not funding COX-2 inhibitors for chronic arthritis

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Abstract

COX-2 inhibitors have come under a lot of scrutiny lately, with questions raised regarding class effects and the risk-benefit of these pharmaceuticals. From 1999 to 2003 the New Zealand Pharmaceutical Management Agency (PHARMAC) evaluated the evidence on COX-2 inhibitors, including their efficacy, cost-effectiveness and budgetary impact. In September 2003 PHARMAC decided not to list celecoxib, rofecoxib and meloxicam on the Pharmaceutical Schedule. This decision meant that at least 18 other pharmaceuticals were able to be funded or have access extended, resulting in 437 ‘statistical lives’ saved per year, with net health gains, and savings for District Health Boards. Had PHARMAC funded COX-2 inhibitors at the same time as Australia, it is estimated that this may have resulted in approximately 740 to 4220 excess myocardial infarctions (MIs) and approximately 330 to 1900 excess deaths from MI.

Drugs: cyclo-oxygenase 2 (COX-2) inhibitors—celecoxib (Celebrex) and rofecoxib (Vioxx).

Indication: pain and inflammation in osteoarthritis (OA) and rheumatoid arthritis (RA).*

Recommended dose: rofecoxib 25 mg per day; celecoxib 200 mg per day.

Clinical efficacy and safety

Two large pivotal trials have been conducted to assess the effectiveness of celecoxib and rofecoxib compared with conventional nonsteroidal anti-inflammatory drugs (NSAIDs) in reducing gastrointestinal (GI) complications - the Celecoxib Long-term Arthritis Safety Study (CLASS)\(^1\) and Vioxx Gastro-selective Outcomes Research (VIGOR) study.\(^2\)

These two trials found that COX-2 inhibitors are no more effective than conventional NSAIDs in reducing pain and improving physical and global functions in both OA and RA patients, but may be associated with a lower rate of GI complications and improved tolerability. However, it has been widely questioned whether the claims over GI safety were overstated, particularly as, controversially, only the more positive 6-month CLASS results were reported even though the 12-month results were available.\(^3\)\(^-\)\(^8\)

The cardiovascular safety of COX-2 inhibitors has also been questioned since the VIGOR trial was published in 2000.\(^3\)\(^,\)\(^9\)\(^,\)\(^10\) This trial found a five-fold incidence of myocardial infarction (MI) in patients administered rofecoxib compared with the naproksen group (0.5% vs. 0.1% respectively).\(^11\)
These cardiovascular concerns were confirmed when rofecoxib was abruptly withdrawn from the market in October 2004, following the results of the Adenomatous Polyp Prevention on Vioxx (APPROVe) trial indicating an increased risk of confirmed serious thrombotic events (including MI and stroke) in long-term use.\textsuperscript{12,†}

A cumulative meta-analysis published in December 2004 based on 18 RCTs reported a relative risk of MI with rofecoxib of 2.24 (95% CI 1.24–4.02). The authors concluded that rofecoxib should have been withdrawn several years earlier.\textsuperscript{35}

It was later estimated that rofecoxib could have caused 88,000–140,000 excess cases of serious coronary heart disease in the United States, many of which were likely to have been fatal.\textsuperscript{13} If COX-2 inhibitors were funded in New Zealand, we estimate that this would have resulted in between 740 and 4220 additional MIs, with 330 to 1900 excess deaths from MI.‡

It seems likely that the increased cardiovascular risk is a class effect of COX-2 inhibitors.\textsuperscript{14,15} The evidence on COX-2 inhibitors, including their cardiovascular risk, was thoroughly reviewed by the Medicines Adverse Reactions Committee (MARC) in early 2005. The Committee concluded that there was an overall class effect for cardiovascular risk with COX-2 inhibitors, and that given the limitations of the available data, all COX-2 inhibitors should be treated comparably and any restrictions placed on the products should be similar across the range of products (http://www.medsafe.govt.nz/profs/adverse/minutes121.htm).\textsuperscript{16}

**Background to PHARMAC’s Decision**

PHARMAC first received an application to list celecoxib in 1999. An application for the listing of rofecoxib was received in 2000. As with all applications PHARMAC receives, these applications were reviewed by PHARMAC’s Pharmacology and Therapeutic Advisory Committee (PTAC).§

PTAC considered that the place in therapy and safety profile of COX-2 inhibitors still needed to be fully elucidated from post-marketing experience. The committee considered that COX-2 inhibitors were expensive and agreed that the additional expenditure over NSAIDs could not be justified considering the modest decrease in serious GI complications. In addition, the committee considered that patients at high risk of adverse events, including gastro-intestinal ones, would still have to be considered at high risk if treated with COX-2 inhibitors, hence targeting specific subgroups of patients would be difficult. However, at the time, PTAC considered that there was no clinical reason not to list these pharmaceuticals, hence PHARMAC staff continued to evaluate these drugs.

A rapid economic analysis was undertaken in 2002 to assess whether the benefits of COX-2 inhibitors (in terms of any reduction in GI bleeds) would compensate for the substantially higher price, compared with other pharmaceuticals PHARMAC has funded. This rapid analysis indicated that this class of drugs was not cost-effective when compared with other pharmaceuticals PHARMAC had funded. The analysis also indicated that given the available budget they were unaffordable.

PHARMAC and PTAC continued to keep up-to-date with the growing amount of international literature regarding the efficacy and safety profile of COX-2 inhibitors...
and were aware of the increasing cardiovascular concerns associated with COX-2 inhibitors.

In 2003 PHARMAC was asked to share its work on COX-2 inhibitors with District Health Board (DHB) hospitals. A summary discussion document was written and distributed to DHB hospitals in April 2003 (http://www.pharmac.govt.nz/pdf/Cox2.pdf) highlighting the clinical evidence, cardiovascular concerns, cost-effectiveness and economic impact of COX-2 inhibitors.17

In September 2003 PHARMAC consulted with medical groups, pharmaceutical suppliers and interested parties on a proposal not to fund COX-2 inhibitors. Following this consultation, the PHARMAC Board resolved to decline the listing of celecoxib, rofecoxib and meloxicam on the Pharmaceutical Schedule.

**Government Policy**

PHARMAC's objective, as outlined in the NZ Public Health and Disability Act 2000, is to secure for eligible people in need of pharmaceuticals, the best health outcomes that are reasonably achievable from pharmaceutical treatment and from within the funding provided.18

PHARMAC evaluated the evidence on COX-2 inhibitors, including efficacy and cost-effectiveness. PHARMAC also calculated that funding COX-2 inhibitors would exceed $30 million per year. Based on this evidence PHARMAC concluded that for all patients that the cost of COX-2 inhibitors was significant and the benefits relatively minimal when compared with other pharmaceuticals awaiting funding.

PHARMAC must work within a fixed budget. Had COX-2 inhibitors been funded, then for the relevant time period this would have meant not funding or extending access for at least 18 pharmaceutical treatments, including extending access to statins and alendronate, venlafaxine, leflunamide, newer antiepileptic agents, and 3/4ths of extending access to olanzapine.** We calculate that by funding these pharmaceuticals rather than COX-2 inhibitors, the equivalent of 437 ‘statistical lives’ were saved per year†† (i.e. if COX-2 inhibitors had been funded then the equivalent of 437 lives would have been lost per year from not receiving other pharmaceutical treatments).‡‡ These investments also nominally saved an extra $17 million to the health sector; funding COX-2 inhibitors would have meant not realising these nominal savings.§§ Overall, the decision not to fund COX-2 inhibitors ultimately resulted in greater health gains from the pharmaceutical budget than would have been achieved otherwise. In fact, if COX-2 inhibitors were funded, this would have achieved a small net health loss, due to excess MIs.†††

**Economic Analysis**

In early 2002 PHARMAC staff undertook a rapid economic analysis for celecoxib using the 6-month CLASS data (indicative results described above).19 A detailed analysis on celecoxib and rofecoxib was then completed for PHARMAC in December 2003.

The results of the detailed analysis indicated that the cost per quality adjusted life year (QALY) of COX-2 inhibitors (celecoxib and rofecoxib) compared with conventional
NSAIDs for patients with a high-risk of GI haemorrhage\footnote{ was over $1 million. For average risk patients, there was no overall benefit and higher total costs (i.e. negative risk-benefit ratio due to impact of MIs), with -0.00161 QALYs lost per patient per 5 years of treatment. The cost/QALY of celecoxib alone compared with conventional NSAIDs in high-risk patients was $450,000. This suggested that COX-2 inhibitors were not cost-effective compared with other pharmaceuticals that could have been funded at the time.\footnote{§§§ These results are consistent with several other analyses internationally.\footnote{ We acknowledge that COX-2 inhibitors can provide benefits for the subgroup of patients who are at high risk of GI bleeds and cannot tolerate or do not respond to conventional NSAIDs. However, we consider that it is still not cost-effective to fund COX-2 inhibitors for this subgroup when compared with other pharmaceuticals that could be funded – reflecting the trade-offs between improved GI symptoms and sequelae versus cardiovascular adverse effects. As well, these patients are still at risk of GI haemorrhage with COX-2 inhibitors, and as PTAC noted previously, targeting would be difficult.}

\textbf{Current Situation: New Zealand}

There are currently five COX-2 inhibitors available in New Zealand – celecoxib (Celebrex), etoricoxib (Arcoxia), meloxicam (Mobic), lumircoxib (Prexige), and parecoxib (Dynastat).\footnote{ The Medicine Adverse Reactions Committee (MARC) has examined the evidence on the safety of COX-2 inhibitors, and recommended that they stay on the market but with considerably stronger warnings and requirements by pharmaceutical suppliers to collect and report information on their usage.\footnote{ These recommendations have been accepted by the Ministry of Health. This decision was based on the argument that for some patients these medicines are the best treatment option. However the stronger warnings reflect MARC’s view that an increased risk of heart attacks and strokes can occur with all COX-2 inhibitors. This decision was consistent with recommendations made by the European Medicines Evaluation Agency, and the Australian Therapeutic Goods Administration. COX-2 inhibitors are being used in New Zealand despite PHARMAC not funding them. COX-2 inhibitors are funded by ACC (PHARMAC understands this to be in the region of $1.1 million per year), whilst Pfizer has been reported as estimating that 11,600 patients received celecoxib during 2004.\footnote{}}

Current Situation: International

\textbf{Australia}

In Australia celecoxib and rofecoxib were listed on the Pharmaceutical Benefits Scheme (PBS) in August 2000. The rapid uptake of celecoxib and rofecoxib following their listing was unprecedented—800,000 prescriptions were written in the first 30 days, and 1.5 million prescriptions were written by the end of the first four months. This had a significant effect on the health budget, costing Aus$205 million in
the 2000/01 financial year.\textsuperscript{29} COX-2 inhibitors were identified as a major reason for the health budget blowout in Australia in 2002.\textsuperscript{30,31}

Following the withdrawal of rofecoxib, the Therapeutic Goods Administration (TGA) undertook an urgent evaluation of COX-2 inhibitors.\textsuperscript{32} The results of this review were considered by the Australian Drug Evaluation Committee (ADEC), which made a number of recommendations to restrict the use of these drugs in Australia, including the introduction of explicit warnings in product information about the increased risk of cardiovascular adverse events. It also recommended that COX-2 inhibitors be prescribed only when other treatments cannot be tolerated or have caused serious adverse effects. In addition, celecoxib and meloxicam should not be prescribed to patients with increased risks of cardiovascular events and treatment should be limited to the shortest time needed. The TGA is also advising patients to review their treatment and dosage regime with their doctor.

Dispensings for COX-2 inhibitors in Australia during July 2005 (n=155,321) were 31\% of their levels during the beginning of 2004.\textsuperscript{29}

**Europe**

The European Medicines Agency (EMEA) recommended the suspension of the marketing authorisation for valdecoxib (Bextra) and new contraindications and warnings for other COX-2 inhibitors:\textsuperscript{33,34}

- A contraindication introduced for all COX-2 inhibitors in patients with ischemic heart disease or stroke;
- A warning introduced for prescribers to exercise caution when prescribing COX-2 inhibitors for high risk patients;
- Doctors are advised to used the lowest effective dose for the shortest possible duration of treatment;
- Additional or strengthened warnings regarding risk of hypersensitivity reactions.

**Comment**

PHARMAC will continue to review the evidence on new pharmaceuticals, to try to ensure that maximum health gains can be obtained from the budget available.

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Endnotes:

*PHARMAC has not assessed COX-2 inhibitors for use post-operatively.

†The APPROVe study was a multi-centre, randomised, placebo-controlled, double-blind study to determine the effect of 3 years treatment with rofecoxib on the recurrence of neoplastic polyps of the large bowel in 2600 patients with a history of colorectal adenoma. In this study 25 patients taking placebo versus 45 patients taking rofecoxib experienced a confirmed serious thrombotic event. The absolute event rates were approximately 3 per 400 patient years for placebo and 6 per 400 patient years for rofecoxib, i.e. an absolute increase in risk of approximately 3 thrombotic events per 400 patient years of treatment. The difference in event rates was only apparent after 18 months of treatment.

‡This estimate is based on uptake patterns in Australia. Between August 2000 (when celecoxib was funded on the Pharmaceutical Benefits Scheme (PBS)) and October 2004 (when rofecoxib was withdrawn) there were 25,101,929 dispensings for celecoxib and rofecoxib in Australia (PHARMAC analysis of PBS services and cost data at [http://www.hic.gov.au/statistics/dyn_pbs/forms/pbs_tab1.shtml](http://www.hic.gov.au/statistics/dyn_pbs/forms/pbs_tab1.shtml)). Had New Zealand funded COX-2 inhibitors at the same time, the total usage of COX-2 inhibitors over the 51 month time period would have been 416,518 person-years. It is assumed that 50% of usage would be for rofecoxib and 50% celecoxib. The estimate does not take into account the number of patients in New Zealand who were taking COX-2 inhibitors at the time (either funded by ACC or self-funded). The proportion of patients administered various NSAIDs was based on script data between 2001-2002 financial year. Excess cases of MI were calculated using methods similar to those of Graham et al [Lancet 2005;359:475-81]. The relative risk of MI with rofecoxib (RR 2.24) is based on the results of the Juni et al. meta-analysis on 18 RCTs on rofecoxib [Lancet 2004;364:2021-9], and the relative risk of MI with celecoxib (RR 1.4) was based on the results of the Moore et al meta-analysis [Arthritis Res Ther 2005;7:R644-65]. The (weighted-average) risk of MI for patients administered NSAIDs was calculated from the VIGOR and CLASS trials and the TennCare observational study [(Ray et al. Lancet 2002;359:118-23]. The analysis assumes case fatality rates for MI of 44-45% [sources: NZ 28-day case fatality rate calculated from Auckland Regional Coronary Outcomes Study (ARCOS) data (Robert Beaglehole and Alistair Stewart, personal communication 1996), registrants aged 35 to 64 years 1986 to 1992 (no. deaths with 28 days / no. registrants); United Kingdom Heart Attack Study Collaborative Group (Norris RM. BMJ 199;316:1065-70; American Heart Association statistics cited by Graham et al Lancet 2005].

§PTAC is a group of clinicians that considers clinical evidence and provides independent and objective advice to PHARMAC on the clinical consequences of funding decisions. [http://www.pharmac.govt.nz/ptac.asp](http://www.pharmac.govt.nz/ptac.asp)

**This analysis calculates that, based on Australian uptake rates, expenditure in the first year may have been NZ$33.4 million (PHARMAC analysis of PBS data with 4,594,187 COX-2 inhibitor dispensings in the first 12 months in Australia; assumes $1.20/patient/day cost). This compares with 18.7 pharmaceutical investments between 1999/00 to 2003/04 giving the same estimated spending over the first 12 months. These investments, in order of total quality-adjusted life years (QALYs) gained during the first 12 months that they were funded, were: statins; alendronate and etidronate for severe osteoporosis; levonorgestrel-releasing intrauterine devices and tranexamic acid for heavy menstrual bleeding; imatinib for chronic myeloid leukemia + GIST; lamivudine for chronic Hepatitis B infection; venlafaxine for refractory depression; 3/4ths of olanzapine for schizophrenia; letfinumide for rheumatoid arthritis; naltrexone for alcohol addiction; topiramate and gabapentin for refractory epilepsy; anastrazole for advanced breast cancer; etanercept for juvenile rheumatoid arthritis; tacrolimus for immunosuppression post any organ transplant; eformoterol (LABA) for asthma.

††In this context, each ‘life saved’ is a statistical life, and each saved life is equivalent to living a full quality of life for 36.4 remaining years expected for the average New Zealand citizen. The present value is 9.7 years after discounting at 10% (the discount rate used by PHARMAC for economic analyses for decisions up until July 2005). ‘Statistical lives’ are calculated from total quality-adjusted life years (QALYs) estimated for decisions, by dividing total QALYs by the above 9.7 discounted years lost prematurely per average death. Further information about QALYs is available at [http://www.nzma.org.nz/journal/116-1170/362/](http://www.nzma.org.nz/journal/116-1170/362/) and [http://www.pharmac.govt.nz/pdf/QALYExplanation.pdf](http://www.pharmac.govt.nz/pdf/QALYExplanation.pdf)
In this analysis approximately 4,231 QALYs would have been lost in the first 12 months alone had PHARMAC not funded the 18.7 new investments but had instead funded COX-2 inhibitors. This equates to 906 QALYs per million population per year. This estimate does not take into account patients in New Zealand who were taking COX-2 inhibitors at the time (either funded by ACC or self-funded).

According to PHARMAC’s economic analyses for the 18.7 investments, spending the $33.4 million over the first 12 months would mean fewer health sector costs elsewhere through reduced use of other pharmaceuticals, hospitalisations, disability support services, etc., to the tune of $17.0 million (i.e. offsets of 51%). Hence the net cost to DHBs of these 18.7 investments was $16.4 million over the first 12 months. By contrast, funding COX-2 inhibitors would have meant savings to the health sector of $9.3 million through reduced costs of conventional NSAIDs. Hence, the net savings to DHBs through the 18.7 investments rather than COX-2 inhibitors would have been $7.6 million over the first 12 months (the difference between the $17.0 million and $9.3 million, with rounding). This estimate does not take into account patients in New Zealand who were taking COX-2 inhibitors at the time (either funded by ACC or self-funded).

On average perhaps 454 (range 136-772) additional MIs and 204 (60-347) excess deaths from MI during would have occurred in New Zealand during the first year of COX-2 inhibitor funding – using the same methods as earlier in endnote ‡ (based on Graham et al Lancet 2005) and an estimated 76,232 patients predicted to use COX-2 inhibitors in New Zealand within the first 12 months (PHARMAC analysis of PBS services data). Taking into account the number of major GI bleeds prevented from the use of COX-2 inhibitors (approximately 225 – based on the incidence rates in CLASS and VIGOR) this results in an overall risk-benefit ratio of COX-2 inhibitors 2.6:1. However, due to a lower case-fatality rate with major GI bleeds (approximately 12% - see Economic analysis section) compared with MIs (44-45%), the risk-benefit ratio of COX-2 inhibitors in preventing death is 9.9:1 (i.e. patients administered COX-2 inhibitors are approximately 10-times more likely to die from MI compared with a major GI bleed). Hence any QALY gains from fewer GI bleeds would be offset by greater QALY losses from excess MIs. This estimate does not take into account patients in New Zealand who were taking COX-2 inhibitors at the time (either funded by ACC or self-funded).

Patients with a high risk of GI haemorrhage were defined for the purposes of the economic analysis here as persons with a history of GI ulcer events.


Valdecoxib (Bextra) was voluntarily withdrawn in April 2005 due to concerns about an increased risk of serious skin reactions.
References:


18. New Zealand Public Health and Disability Act 2000, Section 47 Objectives of Pharmac...


