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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 gastrointestional (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 trail 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 naproxen 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.[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.[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.[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.[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).[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‡‡‡ 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.[20-24] §§§

These results are consistent with several other analyses internationally.[25-27]

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.

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).****

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.[28] 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.[16]

Current Situation: International

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.[29] COX-2 inhibitors were identified as a major reason for the health budget blowout in Australia in 2002.[30,31]

Following the withdrawal of rofecoxib, the Therapeutic Goods Administration (TGA) undertook an urgent evaluation of COX-2 inhibitors.[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.[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:[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). 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;3365:475-81]. 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

**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; leflunomide 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/ and 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.

§§§Cost/QALYs of other pharmaceuticals that could have been funded at the time (1999/00 to 2003/04) included: Extending access to erythropoetin beta for anaemia of chronic renal failure (2002/2003) $-40,000/QALY; Access for olanzapine for schizophrenia - existing patients with risperidone failure (1999/2000) $-5,748/QALY; Extending access to alendronate for osteoporosis (2003/2004) $-3,395/QALY; Listing of levonorgestrel-releasing IUS for heavy menstrual bleeding (2002/2003) $750/QALY; Listing of lamivudine for chronic Hepatitis B infection (1999/2000) $1,500/QALY; Extending access to tranexamic acid for heavy menstrual bleeding (2001/2002) $2,185/QALY; Extending access to statins for cardiovascular risk (dyslipidaemia) (2001/2002) $2,495/QALY; Listing of alendronate for severe osteoporosis (1999/2000) $3,545/QALY; Listing of naltrexone for alcohol addiction (2003/2004) $3,600/QALY; Extending access to anastrazole for breast cancer (advanced) (2002/2003) $4,000/QALY; Listing of venlafaxine for refractory depression (2003/2004) $4,000/QALY; Extending access to etidronate for osteoporosis (2003/2004) $6,492/QALY; Extending access to alendronate for osteoporosis to 1+# (BMD<-3.0) (2000/2001) $12,426/QALY; Extending access to tacrolimus for immunosuppression post any organ transplant (primary treatment or rescue therapy) (2003/2004) $12,500/QALY; Listing of leflunomide for rheumatoid arthritis (2001/2002) $14,086/QALY; Listing of gabapentin for refractory epilepsy (2000/2001) $15,000/QALY; Listing of topiramate for epilepsy (refractory) (2000/2001) $18,500/QALY; Listing of imatinib for chronic myeloid leukemia + GIST (2002/2003) $18,900/QALY; Extending olanzapine for schizophrenia to new cases (1999/2000) $27,467/QALY; Listing of eformoterol for asthma symptom control (2000/2001) $40,000/QALY; Listing of etanercept for juvenile rheumatoid arthritis (2003/2004) $40,000/QALY.

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

References:

1. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA. 2000 Sep 13;284(10):1247–55.
2. Bombardier C, Laine L, Reicin A, et al; VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. N Engl J Med. 2000 Nov 23;343(21):1520–8, 2 p following 1528.
3. Juni P, Rutjes AWS, Dieppe PA. Are selective COX 2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? BMJ 2002, 324: 1287–8. Available online. URL: http://bmj.bmjjournals.com/cgi/content/full/324/7349/1287 Accessed September 2005.
4. Gottlieb S. Researchers deny any attempt to mislead the public over JAMA article on arthritis drug. BMJ 2001;323:301.
5. Metcalfe S, Dougherty S, McNee W. Celebrex's relative gastrointestional safety is overstated. BMJ 2003. 326: 334–5. Available online. URL: http://bmj.com/cgi/content/full/326/7384/334 Accessed September 2005.
6. Graham DY. NSAIDs, Helicobacter pylori, and Pandora's Box. N Engl J Med. 2002;347:2162–4.
7. [No authors listed] Rofecoxib in rheumatoid arthritis: new indication. No better that other NSAIDS. Prescrire Int. 2003 Jun;12(65):89–90.
8. Therapeutics Initiative British Columbia. Therapeutics Letter 43. November / December 2001 & January 2002. COX-2 inhibitors update: Do journal publications tell the full story? Available online. URL: http://www.ti.ubc.ca/pages/letter53.htm Accessed September 2005.
9. Therapeutics Initiative British Columbia. Therapeutics Letter 39. January / February 2001. Selective COX-2 inhibitors: Are they safer NSAIDs? Available online. URL: http://www.ti.ubc.ca/pages/letter39.htm Accessed September 2005.
10. Wright JM. The double-edged sword of COX-2 selective NSAIDs. CMAJ. 2002 Nov 12;167(10):1131–7. Available online. URL: http://www.cmaj.ca/cgi/content/full/167/10/1131 Accessed September 2005.
11. Targum SL. Food and Drug Administration: cardiovascular safety review rofecoxib. 2001. Available online. URL: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_06_cardio.pdf Accessed September 2005.
12. Bresalier RS, Sandler RS, Quan H, et al. Adenomatous Polyp Prevention on Vioxx (APPROVe) Trial Investigators. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med. 2005 Mar 17;352(11):1092–102.
13. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study. Lancet. 2005 Feb 5-11;365(9458):475–81.
14. Weatherall M, Aldington S, Shirtcliffe P, et al. COX-2 inhibitors—first, do no harm. N Z Med J. 2005 Mar 11;118(1211). URL: http://www.nzma.org.nz/journal/118-1211/1359/
15. Solomon SD, McMurray JJ, Pfeffer MA, et al; Adenoma Prevention with Celecoxib (APC) Study Investigators. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med. 2005 Mar 17;352(11):1071–80. Epub 2005 Feb 15.
16. Minutes of the 121st Medicines Adverse Reactions Committee meeting, 15th March 2005. Available online. URL: http://www.medsafe.govt.nz/profs/adverse/minutes121.htm Accessed September 2005.
17. PHARMAC Discussion Document. Celecoxib (Celebrex) and rofecoxib (Vioxx) – selective cox-2 inhibitors – for osteoarthritis and rheumatoid arthritis. February 2004. Available online. URL: http://www.pharmac.govt.nz/pdf/Cox2.pdf Accessed September 2005.
18. New Zealand Public Health and Disability Act 2000, Section 47 Objectives of Pharmac

19. Rafter N. Milne R. Jackson R. PHARMAC Technology Assessment Report No. 55 – Listing rofecoxib and celecoxib in the Pharmaceutical Schedule. 2003 (unpublished).
20. PHARMAC. Report of the Pharmaceutical Management Agency Limited for the year ended 30 June 2000. Presented to the House of Representatives pursuant to Section 44A of the Public Finance Act 1989. PHARMAC, 2000. Available online. URL: http://www.pharmac.govt.nz/pdf/Annual_Report_2000.pdf Accessed September 2005.
21. PHARMAC. Annual Report of the Pharmaceutical Management Agency for the year ended 30 June 2001. Presented to the House of Representatives pursuant to Section 44A of the Public Finance Act 1989. PHARMAC, 2001. Available online. URL: http://www.pharmac.govt.nz/pdf/AnnRep01.pdf Accessed September 2005.
22. PHARMAC. Annual Report of the Pharmaceutical Management Agency for the year ended 30 June 2002. Presented to the House of Representatives pursuant to Section 44A of the Public Finance Act 1989. PHARMAC, 2002. Available online. URL: http://www.pharmac.govt.nz/pdf/Annual%20Report%202002.pdf Accessed September 2005.
23. PHARMAC. Annual Report of the Pharmaceutical Management Agency for the year ended 30 June 2003. Presented to the House of Representatives pursuant to Section 44A of the Public Finance Act 1989. PHARMAC, 2003. Available online. URL: http://www.pharmac.govt.nz/pdf/ARep03.pdf Accessed September 2005.
24. PHARMAC. Annual Report of the Pharmaceutical Management Agency for the year ended 30 June 2004. Presented to the House of Representatives pursuant to Section 44A of the Public Finance Act 1989. PHARMAC, 2004. Available online. URL: http://www.pharmac.govt.nz/pdf/AR04.pdf Accessed September 2005.
25. Maetzel A. Krahn M. Naglie G. The cost-effectiveness of celecoxib and rofecoxib in patients with osteoarthritis or rheumatoid arthritis. Canadian Coordinating Office for Health Technology Assessment 2001. Technology Report No. 23. Available online. URL: http://www.ccohta.ca/ Accessed September 2005.
26. Spiegel B. Targownik L. Dulai G. Gralnek I. The cost-effectiveness of cyclooxygenase-2 selective inhibitors in the management of chronic arthritis. Ann Int Med 2003;138(10):795–806.
27. Cox ER. Motheral B. Mager D. Verification of a Decision Analytic Model Assumption Using Real-World Practice Data: Implications for the Cost Effectiveness of Cyclo-oxygenase 2 Inhibitors (COX-2s). Am J Managed Care 2003; 9(12):785–94
28. Medsafe media release. Stringent conditions for cox-2 inhibitors. April 2005. Available online. URL: http://www.medsafe.govt.nz/hot/media/2005/COX2April05.htm Accessed September 2005.
29. PHARMAC analysis of PBS services and cost data at http://www.hic.gov.au/statistics/dyn_pbs/forms/pbs_tab1.shtml (codes 8439E, 8440F, 8471W, 8472X, 8473Y, 8474B)
30. Dowden JS. Coax, COX and cola. Med J Aust. 2003 Oct 20;179(8):397–8.
31. Prescribing Practice Review 16. Cox-2 selective NSAIDs. National Prescribing Service Limited. 2001.
32. Therapeutic Goods Administration. Expanded information on cox-2 inhibitors for doctors and pharmacists. February 2005. Available online. URL: http://www.tga.gov.au/media/2005/050214_cox2.pdf Accessed September 2005.
33. European Medicines Agency. Public statement, European Medicines Agency announces regulatory action on cox-2 inhibitors. Available online. URL: http://www.emea.eu.int/pdfs/human/press/pr/6275705en.pdf Accessed September 2005.
34. European Medicines Agency. Press release, European Medicines Agency concludes action on cox-2 inhibitors. Available online. URL http://www.emea.eu.int/pdfs/human/press/pr/20776605en.pdf Accessed September 2005.
35. Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet. 2004 Dec 4-10;364(9450):2021-9. Available online. URL:

http://www.thelancet.com/journals/lancet/article/PIIS0140673604175144/fulltext Accessed September 2005.