

Hospital Pharmaceutical Assessment Final Summary Discussion Document No. 6

Celecoxib (Celebrex) and rofecoxib (Vioxx) - selective COX-2 inhibitors - for osteoarthritis and rheumatoid arthritis

Summary

- ⇒ Celecoxib and rofecoxib are anti-inflammatory, analgesic and anti-pyretic agents that act via selective inhibition of cyclooxygenase-2 (COX-2). They are indicated for the treatment of pain and inflammation in osteoarthritis and rheumatoid arthritis.
- ⇒ Two large pivotal trials have been conducted to assess the effectiveness of celecoxib (CLASS) and rofecoxib (VIGOR) compared with conventional nonsteroidal anti-inflammatory drugs (NSAIDs) in reducing gastrointestinal (GI) complications.
- ⇒ COX-2s are no more effective than conventional NSAIDs in reducing pain, but may be associated with a lower rate of GI complications. However, there is evidence that this benefit is reduced with the co-administration of aspirin.
- ⇒ There is an increasing amount of evidence to suggest that some COX-2 selective inhibitors may have the potential to increase the risk of cardiovascular events compared to conventional NSAIDs.
- ⇒ The cost/QALY of celecoxib compared with conventional NSAIDs is estimated to be at least \$60,000-\$220,000 (depending on population risk of GI ulcer), with no overall benefit seen in celecoxib compared with diclofenac, or rofecoxib compared with naproxen.
- ⇒ COX-2 inhibitors provide little (if any) additional clinical benefit over traditional NSAIDs and at significantly higher cost. The net cost of funding celecoxib would be approximately \$30 million per year.

Why produce this discussion document?

At the November 2002 meeting of PHARMAC's Hospital Pharmaceutical Advisory Committee (HPAC), members considered that it would be useful for PHARMAC to make available to District Health Boards (DHBs) some of its economic analyses, for pharmaceuticals used as much in hospitals as the community.

One of the most commonly requested analyses by HPAC and DHB hospitals has been for celecoxib (Celebrex[®]) and rofecoxib (Vioxx[®]).

<p>D evelop consensus R educe duplication U ndertake analysis G enerate discussion S hare information</p>
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The focus of this summary document is therefore to highlight for DHBs the cost-effectiveness, effectiveness and safety of the selective COX-2 inhibitors, celecoxib and rofecoxib, compared with conventional nonsteroidal anti-inflammatory drugs (NSAIDs), for the treatment of rheumatoid arthritis and osteoarthritis. The methodology used to construct this summary document is outlined in Appendix 1.

In April 2003, PHARMAC distributed a draft version of this COX-2 inhibitor discussion document for comment. This final version has incorporated or addressed all significant issues that were raised during consultation.

Introduction

NSAIDs are used widely to treat pain and inflammation. There has been a large amount of interest in the new selective cyclooxygenase-2 (COX-2) inhibiting NSAIDs since their introduction. There is a perception that these drugs are less toxic than conventional NSAIDs.

But are these drugs really safer than currently funded NSAIDs? Do they reduce the risk of serious upper gastrointestinal complications as initially claimed? Are the costs of COX-2s justified in terms of their tolerability and safety? Are they cost-effective? Why doesn't PHARMAC fund COX-2s for use in the community? Should hospitals fund them?

This document attempts to answer these questions and explains PHARMAC's stance regarding the funding of COX-2s.

What are COX-2 Inhibitors?

Celecoxib and rofecoxib are new members of the COX-2 inhibitor class of agents¹. These agents act to inhibit prostaglandin synthesis, primarily by selectively inhibiting the COX-2 enzyme. COX-2 is induced in response to inflammatory stimuli, leading to the synthesis and accumulation of inflammatory prostanoids, in particular prostaglandin E₂. This in turn causes inflammation with oedema and pain.

Celecoxib and rofecoxib therefore act as anti-inflammatory, analgesic and anti-pyretic agents by blocking the production of inflammatory prostanoids via COX-2 inhibition.

Celecoxib and rofecoxib are indicated for the treatment of pain and inflammation in osteoarthritis (a chronic degenerative joint disease) and rheumatoid arthritis (a systemic inflammatory disease affecting joints and many other organs), and for acute pain and primary dysmenorrhoea.

¹Another COX-2 inhibitor assessed by PHARMAC is meloxicam. Information and PTAC's assessment of meloxicam is available in Appendix 2.
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What other treatments are available?

Paracetamol is first-line therapy for patients with mild to moderate symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) due to its effectiveness in relieving mild to moderate pain, and its safety profile [4,106].

Conventional NSAIDs (e.g. diclofenac and naproxen) are used in the short-term to control acute inflammatory episodes, and in cases where paracetamol is inadequate. Currently 14 different brands of NSAIDs are subsidised in New Zealand. For patients at risk of a gastrointestinal haemorrhage or gastroduodenal ulcer, a proton pump inhibitor (PPI) such as omeprazole can be added to treatment [15,106].

How much is the Cox-2 market worth?

COX-2 selective inhibitors are among the most heavily advertised drugs in the United States and are significant revenue earners for the pharmaceutical companies.

Merck Sharp and Dohme (MSD) spent US\$161 million (NZ\$347 million) advertising rofecoxib in the United States in 2000. This exceeded the advertising budgets for Pepsi and Budweiser beer [101]. In the same year the sales of rofecoxib quadrupled to US\$1.5 billion (NZ\$3.2 billion). In 2001 sales increased to US\$2.6 billion (NZ\$5.6 billion) [2]. Pfizer sells celecoxib, which had \$3.1 billion (NZ\$6.7 billion) in sales in 2001.

Billions of dollars are being spent on COX-2 selective inhibitors worldwide. Is that investment justified? We examine the answer to this question in this discussion document.

How effective are COX-2s?

COX-2s are no more effective than conventional NSAIDs in reducing pain and improving physical and global functions in both OA and RA patients.

Celecoxib

The Celecoxib Long-term Arthritis Safety Study (CLASS) was an amalgamation of two double-blind RCTs for celecoxib (800 mg/day) involving 8,059 patients, one comparing with ibuprofen (2400 mg/day) over 12 months, the other to diclofenac (150 mg/day) over 15 months. These trials, which were funded by Pharmacia, found

that there was no difference in the effectiveness of celecoxib compared with ibuprofen or diclofenac, in terms of the reduction in pain [38].

Other clinical trials assessing the effectiveness of celecoxib compared with conventional NSAIDs in patients with OA [21,22,40] and RA [41,42] have reported similar results. A Cochrane review also concluded that celecoxib controls the symptoms of RA to a similar degree to that of naproxen, diclofenac, and ibuprofen [20].

Rofecoxib

The Vioxx Gastro-selective Outcomes Research (VIGOR) study was a prospective, randomized, double-blind, one year study, evaluating the efficacy of rofecoxib (50 mg per/day) compared with naproxen (1000 mg per/day) in 8,076 patients with RA. The study found rofecoxib and naproxen to be similar in efficacy, with similar rates of discontinuation [35].

Other clinical trials comparing rofecoxib with conventional NSAIDs in patients with OA and RA over a period of 654 weeks have reported similar results [31,33,34,36,37,65,100]. A Cochrane review also showed that rofecoxib demonstrates similar efficacy as naproxen for RA [64].

Celecoxib versus Rofecoxib

We have identified three RCTs that compared the efficacy of celecoxib and rofecoxib. Geba et al. assessed the relative efficacy of rofecoxib (12.5 and 50 mg), celecoxib (200 mg) and acetaminophen (paracetamol) (4000 mg) in 382 patients with OA over a period of 6 weeks. This study, which was sponsored by MSD, found that patients administered rofecoxib (25 mg) had more effective relief of persistent pain when compared to patients' administered celecoxib or acetaminophen, with a similar safety profile [45].

Gibofsky et al. assessed the relative efficacy of celecoxib (200 mg) and rofecoxib (25 mg) in 475 patients with OA of the knee over a period of 6 weeks [104]. This study found celecoxib and rofecoxib demonstrated similar efficacy, and were significantly better compared with placebo [104].

Bianchi and Brogginì compared the efficacy of celecoxib (200 mg), rofecoxib (25 mg) and nimesulide (100 mg) in 30 patients with OA of the knee for 7 days [105]. The study found that nimesulide was significantly more effective in providing symptomatic relief compared with celecoxib and rofecoxib [105].

The results of these trials do need to be interpreted with caution. It is not clear whether the doses used in these trials are comparable. It has been suggested that celecoxib may have been more effective if the dose was 400 mg [46,47]. Also, the duration of the trials are only between one to six weeks, and the results may change over a longer period of time.

Do COX-2s reduce the risk of serious gastrointestinal complications?

There is varying evidence regarding the effectiveness of COX-2s in reducing gastrointestinal (GI) complications.

The two dominant trials, CLASS (6-months) and VIGOR (9-months), reported reductions in ulcer complications with COX-2s compared with conventional NSAIDs. In the VIGOR trial this difference was statistically significant. In the CLASS trial, the incidence of symptomatic ulcers and ulcer complications combined was significantly less for patients administered celecoxib. However, the full 12-15 month CLASS data found no difference in ulcer complications between celecoxib and existing NSAIDs overall.

The lower GI risks associated with rofecoxib may have been overstated as the VIGOR trial did not allow concurrent use of low-dose aspirin.

Initially it looked as if COX-2s would provide a similar level of pain relief as NSAIDs, but with a reduced risk of gastrointestinal (GI) bleeding; a result that many received eagerly. Short-term RCTs showed fewer cumulative gastroduodenal erosions and endoscopic ulcers with the COX-2 inhibitors (9-15%) than with conventional NSAIDs (41-46%) [6,7].

Further studies, however, began to question the integrity of the original results. New information suggests that previous claims over the GI safety of COX-2s may have been overstated.

Celecoxib

The CLASS study results were published in the Journal of the American Medical Association (JAMA), but only the first six months of data were reported from two trials of longer duration.

The 6-month trial results reported a statistically significant reduction with celecoxib in ulcer complications and symptomatic ulcers combined compared with conventional NSAIDs (8% and 1.2% respectively). However, the reduction in

ulcer complications alone for patients administered celecoxib compared with existing NSAIDS was not found to be statistically significant (0.3% and 0.6%, respectively).

Further, the full 12-15 month results reported no significant difference in ulcer complications between celecoxib and existing NSAIDS (0.5% and 0.6%, respectively). Almost all the ulcer complications that had occurred during the second half of the trials were in the celecoxib group [62,63].

Why the difference between short and long-term data?

The authors of the CLASS study attempted to explain the differences in the short and long-term data by arguing that it was caused by the high dropout rate of patients being administered conventional NSAIDS resulting in a lower rate of GI events in these patients [61]. However, as Peter Juni and colleagues pointed out, the number of dropouts increased gradually over the study period, with no sudden increase after six months, and there was little difference in withdrawals between treatment groups [17].

A concern is that the published data from the CLASS trial have been widely distributed and believed. About 30,000 prints were bought from the publisher, which coincided with their increase in sales of celecoxib [17]. Former JAMA editor-in-chief, George Lundberg, reportedly stated that “for a group of researchers to send incomplete information to a journal for consideration, while knowing that a more complete set will be reviewed by an authority figure like the FDA would seem very strange. That is, unless the time-sensitive marketing advantage of a drug with blockbuster sales potential was so compelling that the manufacturer was willing to take that chance to gain an early mass sales advantage” [18].

In fact, the selective reporting of the 6-month CLASS results was subject to an almost unprecedented editorial in the BMJ, heavily critical of JAMA’s reporting of the CLASS trial results [17]. Juni et al commented on how the authors failed to justify the post hoc changes in trial design, outcomes, and analysis, and provided an unconvincing explanation for reporting only on the six-month follow-up. They stated that “publishing and distributing overoptimistic short term data using post hoc changes to the protocol, while omitting disappointing long-term data of two trials, which involved large numbers of volunteers, is misleading”.

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Concurrent use of aspirin:

Low-dose aspirin might offset any GI benefit of COX-2 inhibitors.

In CLASS, those concurrently taking low-dose aspirin (approximately 21% of patients) did not show any reduction in GI complications with celecoxib compared with conventional NSAIDS (further information in Appendix 3).

Other Evidence

Deeks et al. undertook an industry-funded systematic review and meta-analysis of RCTs comparing celecoxib with conventional NSAIDS or placebo. The authors reported equivalent efficacy between celecoxib and conventional NSAIDS, but significantly greater tolerability in terms of withdrawals from the trials as a result of GI complications including symptomatic ulcers, perforation, and haemorrhage [28].

However, the Deeks meta-analysis has proved controversial [72], mainly as it did not use the 12-15 month CLASS data that were reported to the FDA [29, 30]. PHARMAC staff went on to apply the full CLASS data to the Deeks analysis, and found that these made a substantial difference to the GI safety profile of celecoxib [29].

Further information on PHARMAC’s analysis, and key findings of CLASS and other clinical trials on celecoxib, is included in Appendix 3.

In a prominent RCT, published after Deeks meta-analysis, Chan et al looked at the use of COX-2s in patients with a history of recent ulcer bleeding. They found the risk of recurrent bleeding was high regardless of treatment (4.9% of those using celecoxib and 6.4% using diclofenac-plus-omeprazole had recurrent bleeding within six months). The authors suggested that neither regimen could completely protect patients at high risk from recurrent ulcer complications [24]. An accompanying editorial stated that the results were unexpected, with neither regimen providing a good or even acceptable level of protection from recurrent ulcer bleeding. “It is clear that our current strategy for the prevention of NSAID-related ulcers and ulcer complications requires reexamination and revision”[70].

Rofecoxib

The VIGOR study demonstrated that rofecoxib was associated with a lower incidence of complicated ulcers compared with naproxen

(0.4% compared with 0.9%, respectively). The risk of a complicated GI event was estimated to be 1.37 per patient per year with naproxen and 0.59 with rofecoxib ($p=0.005$) [35].

These results need to be interpreted with caution as they may not be replicated in postmarket use for the following reasons:

1. patients in the VIGOR trial were not able to be administered aspirin concurrently, hence the benefit of rofecoxib may be overstated (as aspirin was shown to offset GI benefit of COX-2 inhibitors in the CLASS trial);
2. the comparator used in the VIGOR trial was naproxen, and some argue that diclofenac and ibuprofen are associated with a lower risk of gastrointestinal complications, and hence are the more relevant comparator [17];
3. the difference in GI events emerged only after one month of treatment, indicating that rofecoxib may not reduce GI risk during short-term treatment [106];
4. patients in poor general health were ineligible for the VIGOR trial, hence results cannot be extrapolated to their situation [106].

Laine et al. performed a post hoc analysis on serious lower and upper GI events in the VIGOR trial. They found that the risk of serious lower GI events was 54% lower for patients administered rofecoxib compared with naproxen [43]. The number needed to treat with rofecoxib instead of naproxen to prevent one GI event was 10-12 in the highest risk patients (prior event, age ≥ 75 years, or severe rheumatoid arthritis), 17-33 in patients with other risk factors, and 42-106 in low-risk patients [44].

It should be noted that patients who were administered NSAIDs in the CLASS and VIGOR trials were maintained on the maximum dose of the NSAIDs, rather than having their dose reduced to the minimum effective dose, as is done in clinical practice. Patients therefore had an elevated risk of GI complications [4].

Appendix 3 describes GI effects in two other rofecoxib trials.

Is there an increased risk of cardiac or renal events associated with COX-2s?

The CLASS trial found that there was no significant difference between the treatment groups in the incidence of major cardiovascular events. However, the VIGOR trial reported a four-fold increase of myocardial infarction in patients administered rofecoxib.

There is growing international concern regarding links between COX-2 inhibitors and an increased risk of serious adverse cardiac events. This is a subject of ongoing debate [49,51,52,53,54,55,67].

Small, short-term trials have reached different conclusions regarding the effect of COX-2 inhibitors on cardiac events. One study found that the prevalence of cardiac events was similar in patients prescribed celecoxib and rofecoxib [54], another found that prevalence was lower in patients administered celecoxib compared with rofecoxib [49], and a recent trial found that COX-2s potentially may benefit those with cardiovascular disease [55].

Mukherjee et al. performed a meta-analysis to investigate the effect of COX-2s on cardiovascular events. The review found that there was a potential increase in cardiovascular events with the use of COX-2 inhibitors [51].

Data from the FDA Adverse Event Reporting System (AERS) indicates that rofecoxib and celecoxib are associated with rates of renal failure similar to conventional NSAIDs. However, this has been debated in the literature [56,57,58,59,60].

Celecoxib

In the CLASS trial, in which 21 percent of patients took aspirin, there was no significant difference between the treatment groups in the incidence of major cardiovascular events.

White et al. analysed data from the CLASS trial to determine the incidences of serious cardiovascular thromboembolic events for all patients as well as the subgroup of patients who were not administered aspirin concurrently. They found that the incidence of serious cardiovascular thromboembolic events was not significantly different for all patients administered celecoxib or conventional NSAIDs, and for the subgroups of patients not taking aspirin [23].

Rofecoxib

In the VIGOR study, patients administered rofecoxib had a four-fold increase in myocardial infarctions compared with patients on the conventional NSAID naproxen (0.1% vs 0.4%, respectively). Serious thrombotic events were twice as high in the rofecoxib group (RR 2.38), although these data were not reported in the VIGOR publication. This increase in thrombotic cardiovascular events was found to be significantly higher in all patients administered rofecoxib (including patients who were not needing aspirin).

Why the difference in results?

The fact that the VIGOR trial found a statistically significant difference in major cardiovascular events, and the CLASS trial did not, may have been due to differences in study patients between the trials (the CLASS trial had a higher proportion of patients with OA, and patients with RA have an increased risk of thrombotic events); the use of aspirin by some patients in the CLASS trial; or the nature of the comparator NSAID used in the trials (naproxen – the comparator NSAID in the VIGOR trial – may be protective against cardiovascular events)[26].

Interaction with Warfarin, Ace Inhibitors and Diuretics

The interaction between COX-2 inhibitors and warfarin can cause serious haemorrhagic events. The interaction between COX-2 inhibitors, ace inhibitors and diuretics can cause renal failure and impairment at a similar rate to conventional NSAIDs.

The interaction between COX-2 inhibitors and warfarin can cause serious haemorrhagic events by increasing the international normalised ratio (INR) by approximately 10% [10,26,48,110]. This was raised as a concern by New Zealand's Medicines Adverse Reactions Committee (MARC) [10].

In June 2002, the Centre for Adverse Reactions Monitoring (CARM) released an article outlining the dangers of combining ace inhibitors, NSAIDs and diuretics, due to the effect the combination may have on renal failure and impairment [8].

So how safe are COX-2 inhibitors overall?

The incidence of overall serious adverse events in the two key COX-2 trials (CLASS and VIGOR) was higher for COX-2 inhibitors than conventional NSAIDs. The absolute risk increase was 1-1.5% and the number needed to treat to cause one harmful event was between 67 and 100.

The view that COX-2s are 'safe' to use in those patients for whom conventional NSAIDs would normally be prescribed may not be well founded.

A recent POEM (Patient-Oriented Evidence that Matters) in the BMJ, summarising a recent detailed analysis of safety effects in CLASS and VIGOR [67], stated "The FDA's data show no benefit in terms of gastrointestinal mortality with COX-2 inhibitors, a trend toward greater all-cause mortality, and a significant increase in serious adverse events...COX-2 inhibitors have serious potential harms that have been minimised in reports of research sponsored by drug companies" [66].

Patients who began treatment on celecoxib and rofecoxib in New Zealand between December 2000 and October 2003 are currently being monitored by the Intensive Medicines Monitoring Programme (IMMP). In June 2002, 13 case reports were received of acute psychiatric events for patients administered COX-2 inhibitors [109]. In April 2003, 17 cases of hepatotoxicity associated with COX-2 inhibitors were reported, including 6 cases of significant liver injury [107]. In November 2003, 7 cases of visual disturbance with COX-2 inhibitors were reported by the IMMP in the BMJ, including a case of temporary blindness and a case of a visual field defect [108].

Recovery from these events occurred soon after discontinuing medication. It should be noted that these adverse effects have also been reported with conventional NSAIDs.

Celecoxib

The 6-month data from the CLASS trial reported in JAMA showed that significantly more patients who were administered conventional NSAIDs had nausea, constipation, and hypertension, and significantly more patients who were administered celecoxib had skin reactions including rash and urticaria [38]. However, this report excluded some key safety data.

The 12-15 month CLASS results reported on the FDA website found that there was no significant difference in total serious adverse events² or mortality for patients administered celecoxib compared with other NSAIDs (rate of serious adverse events was 6.8% and 5.8% respectively, mortality rate was 0.4% and 0.43% respectively).

However, in the FDA results there was an increase in other serious events³ for patients administered celecoxib compared with other NSAIDs (5.8% versus 4.8%, respectively), representing an absolute risk increase of 1% and the number needed to treat to cause one harmful event of 100. 22.4% of celecoxib patients and 24.6% of patients on other NSAIDs withdrew due to adverse events.

Deeks' meta-analysis (which used the 6-month CLASS data) found that withdrawals due to all adverse events were not significantly increased with celecoxib compared with placebo or conventional NSAIDs, although withdrawals due to gastrointestinal events were lower from patients administered celecoxib compared with conventional NSAIDs.

Rofecoxib

As with CLASS, only the favourable results of the VIGOR trial were submitted for publication. The article only included discontinuations due to GI events rather than all discontinuations, which favoured rofecoxib.

The total incidence of adverse events was significantly higher for patients administered rofecoxib compared with naproxen (9.3% vs 7.8%, respectively, $p=0.013$), causing an absolute risk increase of 1.5% and a number needed to treat to cause one harmful event of 67 [95,96].

In the FDA results, the number of patients that needed to be withdrawn due to hypertension-related adverse events was significantly higher in the rofecoxib group compared with naproxen (1.0% vs 0.2%, respectively, $p<0.001$) [97].

Even though rofecoxib reduced the incidence of complicated ulcers, the absolute risk reduction was 0.52, where the absolute risk increase from other serious adverse events was 1.5 (mainly due

to an increase in serious cardiovascular adverse events), resulting in an unattractive risk to benefit ratio [96].

What was PTAC's assessment of celecoxib and rofecoxib?

The Pharmacology and Therapeutics Advisory Committee (PTAC) considered applications for celecoxib and rofecoxib between 1999 and 2001. Further details of PTAC's assessment can be found in Appendix 4.

Celecoxib

PTAC considered that celecoxib appears to be similar in effectiveness and safety as other NSAIDs, but may have a better GI safety profile. However, the committee considered that the place of therapy and safety profile of celecoxib still needed to be fully elucidated from post-marketing experience.

The committee considered celecoxib to be expensive and agreed that the additional expenditure over NSAIDs would not be justified considering the modest decrease in serious GI complications. In addition, patients at high risk of adverse events, including gastro-intestinal ones, would still have to be considered at high risk if treated with celecoxib and that, for this reason, PTAC could not recommend targeting to any specific sub-groups of patients.

Rofecoxib

PTAC considered that the efficacy of rofecoxib was comparable with other conventional NSAIDs. The committee considered that rofecoxib had a superior GI safety profile when compared with conventional NSAIDs. However, as with celecoxib, it considered that the true safety profile, particularly in elderly patients at high risk, would only become apparent after considerable post-marketing experience.

The committee considered that concomitant use of low dose aspirin (to provide an anti-platelet effect) is likely to be routine in high-risk cardiac patients and this will reduce the GI safety advantages of rofecoxib. Similarly, an increase in cardiovascular risk associated with rofecoxib in patients not on aspirin will also offset the safety advantages. The committee considered that patients with a high risk of developing upper GI perforations, ulcers and bleeding (PUBs), who are prescribed rofecoxib, might still be prescribed a Proton Pump Inhibitor (PPI).

² Total serious adverse events include death, hospitalisation, or extension of hospitalisation, and any life-threatening event or disability (including complicated ulcers).

³ Other serious adverse events exclude death and complicated ulcer.

The committee considered that the cost offsets in terms of reduction in the use of PPIs in patients with gastrotoxicity induced by conventional NSAIDs might not necessarily be high after they switched to rofecoxib. The committee noted that despite the lack of comparative data there was good evidence suggesting that a combination of PPI with a conventional NSAID protects against further PUBs, and could be used as an alternative approach.

The committee considered that patients at high risk of adverse events, including gastro-intestinal ones, would still be at risk if treated with rofecoxib and that, for this reason, it could not recommend targeting to any specific sub-groups of patients. The committee also considered the price of rofecoxib was disproportionately high compared to its potential benefits.

Has an economic analysis been done in New Zealand?

In early 2002 PHARMAC staff undertook a preliminary economic analysis for celecoxib that utilised the 6month CLASS data. This analysis was referred to in the draft version of this discussion document, and showed that the incremental cost-utility of celecoxib compared with conventional NSAIDs was approximately \$502,000 per quality-adjusted life year (QALY).

A detailed analysis on celecoxib and rofecoxib for the symptomatic relief of OA and RA in patients not receiving aspirin was completed for PHARMAC in December 2003 [119]. This analysis was based on a Markov model developed by the Canadian Coordinating Health Technology Agency (CCOHTA) to assess the cost-effectiveness of celecoxib and rofecoxib over a period of 5 years, using data from the VIGOR and CLASS⁴ trials [68]. The results of the analysis indicated that the cost/QALY of celecoxib compared with conventional NSAIDs is approximately \$60,000-\$220,000 (depending on population risk of GI ulcer), with no overall benefit seen in celecoxib compared with diclofenac, or rofecoxib compared with naproxen.

Note that this report contains only a summary of the full analysis. For a copy of the full analysis, please contact the hospital pharmaceutical analyst at PHARMAC.

Clinical Inputs in Model

The detailed analysis included a systematic review of clinical trials on celecoxib and rofecoxib that showed that the two classes of anti-inflammatories have equivalent efficacy [98], so only the potential for harm from upper GI and MI events were modelled.

The analysis estimated the incremental costs and benefits of rofecoxib versus naproxen, and celecoxib versus diclofenac, and celecoxib versus ibuprofen, in two separate patient groups:

1. all patients with RA or OA;
2. patients at high risk of an upper GI ulcer.

The model was based on the following key assumptions:

Table 1: Key Assumptions used in Model

Effectiveness of COX-2s
Loss of benefit of COX-2s with aspirin
GI Events
OA and RA patients have the same probability of upper GI (UGI) events and MI.
UGI events occur at a constant rate over time.
No significant difference in UGI events and MI for low or high doses of COX-2s [90].
No significant difference in the probability of a UGI event for patients receiving a non-NSAID analgesic (e.g. paracetamol) or a COX-2 inhibitor [68,114,115].
All symptomatic ulcers are treated for 3 months with PPIs and 100% are cured.
Mortality rates among patients with complicated UGI events are independent of the model of therapy (medical or surgical), hence an overall mortality rate was used.
The COX-2 doses that are modelled are those that are indicated as maintenance therapy in RA and OA [117,118]. These are lower than the doses used in VIGOR and CLASS. The analysis assumes that the safety profiles of COX-2s are identical at high and usual doses, although this may be an optimistic assumption.
MI Events
All patients who have an MI and survive are hospitalised.
NSAIDs are assumed not to be cardio-protective.
Other
Non-compliance with analgesic use was not modelled (the systematic review found no significant difference in withdrawal).

⁴ The analysis was based on the 12- and 15-month CLASS data.

The detailed analysis incorporated the following events:

Table 2: Event Rates used in Model

Variable	Values	Ref.
GI Events		
Proportion at high risk of UGI events	8% (0-100%)	35, 38
Probability of symptomatic and complicated ulcer in individuals with a history of ulcer	3.3% (2.5-4%)	35, 38
Probability of hospitalisation with a complicated ulcer	63%	82
Probability of surgery if hospitalised	8.5%	68
Probability of retrying NSAIDs after GI bleed	10% (5-15%)	Expert advice
Case fatality following complicated UGI event	11.7% (low value 4.85%)	83, 111, 112
Effectiveness of PPIs in ulcer prophylaxis when receiving conventional NSAID therapy	40%	82, 84
MI Events		
Case fatality following MI	35-56% (age/gender dependent)	85
Probability of a fatal MI occurring outside hospital	62-85% (age/gender dependent)	85
Post MI mortality at age 60	(1/34)exp(0.055*years post MI)	87, 113
Other Events		
Probability of death from any cause	NZ mortality data 1995/96	86

Quality of Life

The baseline quality of life for patients with RA and OA was estimated for the detailed analysis as 0.688 (where 1=perfect health, and 0=death) [68].

The effect of ulcer complications on quality of life was estimated using results reported in a COX-2 economic analysis [88], which were derived from a study of quality of life in peptic ulcer disease. In this study a symptomatic ulcer had a utility of 0.88 (representing severe dyspepsia), a complicated ulcer treated medically in hospital had a utility of 0.49 for 4 days treatment (utility of 0.86 for one 3-month cycle), and a complicated ulcer requiring surgery had a utility of 0.46 (utility of 0.83 for 3-month cycle).

The utility of acute MI was derived from the New Zealand disability weight for treated acute MI [89], and was estimated to be 0.74⁵.

Costs

The following costs were included in the analysis:

Table 3: Costs used in Model

	Cost (NZ\$)
Pharmaceuticals (cost per day)	
Rofecoxib 25 mg od	\$1.20 (\$1-\$2.30)
Celecoxib 200 mg bd	\$1.20 (\$1-\$2.30)
Naproxen 500 mg bd ⁶	\$0.212
Diclofenac 75 mg bd ⁶	\$0.135
Ibuprofen 600mg tds ⁶	\$0.1863
Paracetamol 1g qds ⁶	\$0.0784
Omeprazole 20 mg od ⁶	\$0.827
Hospitalisation Costs	
Fatal MI ⁷	\$2,848
Non-fatal MI ⁷	\$4,188
Inpatient medical treatment for complicated ulcer ⁷	\$2,258
Inpatient surgical treatment for complicated ulcer ⁷	\$4,016
Outpatient Treatment	
Specialist Gastroenterologist visit, initial consultation, excl GST ⁸	\$178
Outpatient gastroscopy, excl. GST ⁹	\$622
GP visit including patient co-payment, excl. GST ¹⁰	\$33

Cost of Cox-2s

The current cost of rofecoxib and celecoxib to a consumer is approximately \$2.01 for rofecoxib 25 mg daily and \$2.20 for celecoxib 200 mg daily. It is likely that the price would be significantly lower if subsidised therefore an arbitrary lower price was chosen as the base case.

Other non-pharmaceutical health sector costs

The cost of a symptomatic ulcer included the cost of a GP visit and two endoscopies. The cost of an outpatient complicated ulcer included the cost of a GP visit, a specialist visit and two endoscopies [116]. The cost of managing coronary artery disease (CAD) was estimated as \$200 per month [90].

⁵ Weighted average of acute MI (0.605) for approximately 6 days (median length of hospitalisation), and 0.75 for the remainder of the 3-month cycle.

⁶ April 2003 Pharmaceutical Schedule

⁷ 2000/01 NZ public hospital weighted DRGs

⁸ Private gastroenterology clinic, Auckland 2003

⁹ Private hospital, Auckland 2003

¹⁰ Statistics New Zealand

So are COX-2 inhibitors cost-effective?

Rofecoxib was found to be associated with higher total costs and fewer benefits compared with naproxen, and celecoxib was found to be associated with higher costs and fewer benefits compared with diclofenac. In patients at average risk of a GI event, the incremental cost-utility ratio (ICUR) of celecoxib compared to ibuprofen is over \$200,000 per QALY. For patients at high risk of a GI event, the ICUR is over \$60,000 per QALY. This suggests that COX-2s do not represent good value for money compared with other pharmaceuticals that could be funded.

Cost effectiveness is frequently measured in terms of the incremental cost-utility ratio (ICUR). This is defined as the difference in net costs divided by the difference in net benefits. This is where benefits are measured in terms of quality-adjusted life years (QALYs) that result from substituting one treatment for another. Net costs include non-pharmaceutical costs borne by other parts of the public health sector.

Table 4: Cost/QALY Results

Pharmaceutical	Comparator	Cost/QALY Result
Average Risk of GI Event		
Rofecoxib	Naproxen	Higher costs and fewer benefits
Celecoxib	Diclofenac	Higher costs and fewer benefits
Celecoxib	Ibuprofen	\$220,000
High Risk of GI Event		
Rofecoxib	Naproxen	Higher costs and fewer benefits
Celecoxib	Diclofenac	Higher costs and fewer benefits
Celecoxib	Ibuprofen	\$68,000

In predominately average risk population, rofecoxib was dominated by naproxen and celecoxib was dominated by diclofenac (i.e. the COX-2s have higher total costs and provide fewer benefits in terms of number of QALYs). Celecoxib compared with ibuprofen had an incremental cost per QALY gained of over \$200,000, and as such is not considered to be cost effective.

For patients at high risk of a GI event, rofecoxib was dominated by naproxen and celecoxib was dominated by diclofenac. The incremental cost per QALY was approximately \$68,000 for celecoxib compared to ibuprofen, indicating that celecoxib is not cost-effective for high-risk populations.

For individuals at high risk of MI, the adverse cardiovascular effects could outweigh any GI-related benefits, especially as patients are likely to be on concurrent low dose aspirin. While the use of low dose aspirin may reduce any adverse cardiovascular effects, it will also reduce any GI-related benefits of COX-2 inhibitors.

In summary, celecoxib and rofecoxib are not cost effective compared with NSAIDs for the symptomatic treatment of RA and OA. At a cost per QALY of over \$60,000, COX-2s are relatively poor value for money compared with other pharmaceuticals that could be funded (refer to Appendix 5 for the cost/QALY of other pharmaceuticals).

As the risk of GI bleeds and MI events increases with age, the results of the analysis on celecoxib compared with ibuprofen were tested to determine how sensitive they were to changes in the age of patients. Varying the age of patients between 45 years and 75 years, caused the cost per QALY to decrease from \$90,000 to \$40,000. Because the incidence of UGI events is higher than MI events, COX-2s provide additional benefits for the older age group, despite the potential for higher MI rates. However, if aspirin is withheld, the MI rates may be higher, and hence the cost/QALY would increase.

The lowest cost per QALY (\$33,000) was obtained in a 2-way sensitivity analysis for celecoxib compared with ibuprofen in elderly patients with a high risk of GI events but less severe arthritis.

The detailed analysis confirms the results of PHARMAC's earlier preliminary analysis, and is consistent with findings internationally. For instance, the Canadian Coordinating Office for Health Technology assessment (CCOHTA) found that that COX-2s are relatively cost-ineffective when used for patients with average risk of GI events, and more cost-effective for patients with a history of UGI events [68]. Note the CCOHTA analysis did include concomitant increases in MI risk with age.

Similarly poor cost-effectiveness was seen in other North American analyses [94]. A recent report in 'The American Journal of Managed Care' suggests that the cost-effectiveness of COX-2 inhibitors may have previously been overestimated [99]. Previous analyses assumed that the use of gastroprotective agents was lower for patients administered COX-2 inhibitors,

however analysis of medical claims data has indicated that this is not the case. Rather, the use of gastroprotective agents was actually higher amongst patients administered COX-2 inhibitors compared with those administered conventional NSAIDs. This resulted in an increase in the cost/QALY by more than \$80,000 [99].

“But Australia funds them.....”

The rapid uptake of celecoxib and rofecoxib following their listing on the Pharmaceutical Benefits Scheme (PBS) in Australia has been unprecedented by any other pharmaceutical. 800,000 prescriptions were written in the first 30 days following PBS listing of celecoxib in August 2000, and 1.5 million prescriptions were written by the end of the first four months [3,101].

Recent research indicates that physicians are using COX 2 inhibitors indiscriminately. In Australia, 59% of patients prescribed a COX-2 inhibitor for the first time had not received a prescription for a conventional NSAID in the previous 12 months [5]. In Canada, 75% of patients prescribed a COX-2 inhibitor had not had a prescription filled for an NSAID in the 120 days before a COX 2 inhibitor was first prescribed, and 20% had not received an NSAID in five years [71].

When celecoxib was initially listed on the PBS in Australia in August 2000, the projected cost was in the order of \$40m in the first year. Instead it cost over \$170m in the first year, and has continued to increase. COX-2s now cost Australians AUS\$218.6m a year (NZ\$256.3m) [5].

COX-2s were identified as a major reason for the health budget blowout in Australia in 2002 and are now under review.

What effect would funding of these drugs have on the pharmaceutical budget?

PHARMAC’s analysis has indicated that the cost of funding COX-2 inhibitors is likely to be in excess of \$30 million per year.

PHARMAC understands that the private market is in the region of \$10 million per year. This estimate was obtained before the pharmaceutical suppliers began direct-to-consumer advertising (DTCA) of these products, and when celecoxib and rofecoxib were the only COX-2 inhibitors

marketed in New Zealand (valdecoxib and etoricoxib are now available in New Zealand and DTCA is being used extensively). It is therefore likely that the current private for COX-2 inhibitors is in excess of \$10 million per year.

The prevalence of OA and RA in New Zealand is at least 130,000. Considering an annual cost of \$400 per patient, even if only 50 percent of the patient population accessed Cox II inhibitors, the market would increase to \$26 million. Given the likely impact of intensive marketing, this figure could easily be higher.

If the uptake of COX-2 inhibitors in New Zealand was similar to Australia, the gross expenditure could be as high as NZ\$41 million per year (after adjusting for population variances). Accounting for savings from standard NSAIDs, the net cost of Cox II inhibitors in this case would be up to \$35 million per year. Note that Australia restricts DTCA, hence uptake in New Zealand may be higher.

In New Zealand, such large spending would need to come from DHBs’ budgets, and would be at the expense of other health funding priorities.

Will COX-2s ever be funded in the community?

Given the minimal benefits associated with COX-2 inhibitors compared with NSAIDs, the potential for increased risk of cardiovascular events, and the high cost of the drugs, PHARMAC has some reservations about the COX-2 inhibitors.

PHARMAC has decided that on balance we cannot justify subsidising the COX-2 inhibitors at the current price because to do so would compromise our ability to fund other needed medicines and for DHBs to fund other healthcare. If funding were available, other medicines would represent better value for money and have a higher priority.

Therefore, at its October 2003 Meeting, the PHARMAC Board resolved to decline the listing of celecoxib, rofecoxib and meloxicam on the Pharmaceutical Schedule.

Our analyses have indicated that currently the COX-2 inhibitors do not represent an appropriate use of taxpayers’ funds. However, PHARMAC will continue to examine the evidence as it becomes available.

Should hospitals fund them?

This discussion document has highlighted the concerns PHARMAC has regarding COX-2 inhibitors and explains our stance for not funding them. We hope that by sharing this information DHBs will question their reasons for funding (or not funding) COX-2s and discuss the benefits, safety and costs associated with such decisions.

The evidence on COX-2 inhibitors shows that COX-2 inhibitors provide little (if any) additional clinical benefit over conventional NSAIDs. COX-2s are not exempt from the severe GI effects associated with NSAIDs. Assuming equivalent efficacy, the risk to benefit ratio of COX-2 inhibitors depends on the cumulative effects of GI and cardiovascular side-effects, for which the data remain controversial. At present, it is difficult to give an accurate account between the relief of pain and improved function on the one hand, and the likelihood of serious adverse effects on the other [16].

PHARMAC's analyses indicate that the cost-effectiveness of celecoxib and rofecoxib is poor overall compared with conventional NSAIDs, at \$60,000-\$220,000 per QALY.

Conclusion

“Pandora’s box has been opened. We have developed a false sense of security about the protective value of proton-pump inhibitors and COX-2 inhibitors, and now it is clear that the problem needs to be re-examined completely” [70].

To date there is no evidence available suggesting that the COX-2 inhibitors work better than older medicines, such as the conventional NSAIDs.

There is mounting evidence suggesting that the GI profile of the COX-2 inhibitors is not substantially better than that of older medicines such as the conventional NSAIDs. While the relative risk of serious GI complications (perforation, obstruction or bleeding) may be reduced with COX-2 inhibitors, in real terms the absolute risk of such complications is so low that this reduction provides only a very small advantage over other NSAIDs.

There is also an increasing amount of evidence that suggests that some COX-2 inhibitors may

have a potential for increased risk of cardiovascular events compared with conventional NSAIDs. MARC has also raised similar concerns.

This discussion document has outlined the effectiveness, safety, and cost-effectiveness associated with COX-2 inhibitors, and explains PHARMAC’s stance for not funding them.

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Appendix 1 - Methodology

For this review, we searched PubMed, the Cochrane database, the TRIP database (<http://www.tripdatabase.com/>), and various internet sites¹¹. Sites were searched between 19 March and 7 April 2003. We used information from randomised control trials (RCTs), review articles, meta-analyses, guidelines, and economic analyses that were identified in the searches. We also used reference lists of sourced articles to obtain further papers not identified in the above searches; pharmaceutical industry submissions and data supplied to PTAC through PHARMAC. We then undertook a narrative synthesis of the above systematically derived data.

This summary has been reviewed both within PHARMAC and by PTAC members.

Appendix 2 – Meloxicam

Meloxicam (Mobic) is a COX-2 inhibitor that is indicated for the symptomatic treatment of painful osteoarthritis (arthrosis, degenerative joint disease) and symptomatic treatment of rheumatoid arthritis.

Clinical trials have shown that meloxicam has comparable therapeutic efficacy to standard dosages of other NSAIDs such as piroxicam, diclofenac and naproxen and caused fewer gastrointestinal adverse events than those NSAIDs [75,76,77,78,79,80,81].

PTAC considered an application to list meloxicam on the Pharmaceutical Schedule in February 1999 for the treatment of osteoarthritis and rheumatoid arthritis. Further information was considered by PTAC in February 2001. The minutes of the meeting are summarised below:

The committee considered that meloxicam appears to have similar efficacy to other NSAIDs with minor advantages in terms of the incidence of serious gastrointestinal effects. It noted that at a dose of 7.5 mg/day the absolute risk of serious gastro-intestinal side effects was slightly less than diclofenac 100 mg/day and appears similar to other COX-2 inhibitors.

The committee considered that the risk of serious gastro-intestinal events in high-risk patients remained significant with meloxicam and that it could not be assumed that meloxicam may be safely used in patients with risk factors. It considered that patients at higher risk of adverse events, especially gastro-intestinal ones, would still be at higher risk if treated with meloxicam.

¹¹ Other sites searched: Medsafe, CCOHTA, NICE, FDA, Australia Prescriber. Sites were searched between 19 March and 7 April 2003.

Search terms were: celecoxib Limits: Randomized Controlled Trial; celecoxib AND cost*; celecoxib AND rofecoxib; rofecoxib Limits: Randomized Controlled Trial; rofecoxib AND cost*; celecoxib AND economic; rofecoxib AND economic; rofecoxib AND cardiovascular; celecoxib AND cardiovascular; rofecoxib AND warfarin; celecoxib AND warfarin etc.

Appendix 3 – Further Information on GI events

CLASS Trial

The CLASS study results were published in JAMA, but only the first six months of data were reported from two trials of longer duration. One of the trials was a 15-month trial comparing celecoxib with ibuprofen and the other was a 12-month trial comparing celecoxib with diclofenac.

The primary endpoint of the CLASS study, which was published in JAMA, was upper GI ulcer complications. The rate of symptomatic ulcers during the first six months of treatment was also assessed.

The trials reported a statistically significant reduction in ulcer complications and symptomatic ulcers compared with conventional NSAIDs [38]. However, the 12-15 month data show that the risk of complicated ulcers was not significantly different between celecoxib and existing NSAIDs (0.5% and 0.6%, respectively). Almost all the ulcer complications that had occurred during the second half of the trials were in the celecoxib group [62, 63]. The six-month data reported a relative risk reduction (RRR) of 39% in serious upper GI events and endoscopic ulcers for patients administered celecoxib [38]. However, the 12-15 month data showed no statistically significant reduction in relative risk.

The CLASS study also found that those concurrently taking low-dose aspirin (approximately 21% of patients) did not show any reduction in GI complications with celecoxib compared with conventional NSAIDs. The upper GI complication rates for patients who were also administered low dose aspirin was 2.0% for patients administered celecoxib and 2.1% for patients administered ibuprofen/diclofenac. Non-aspirin users who were administered celecoxib had a statistically significant 42% RRR, where aspirin users who were administered celecoxib showed no risk reduction (RR 1.02 (0.59 - 1.74)). The difference between the subgroups' RRRs over the 12-15 months was statistically significant (p 0.03). Therefore, low-dose aspirin may offset any benefit of COX-2 inhibitors.

Other Evidence

Goldstein et al. conducted a pooled analysis of 14 RCTs (11,008 patients) and a separate analysis on an open-label trial (5,155 patients) on celecoxib compared with conventional NSAIDs for patients with RA or OA. In the RCTs, no upper GI events occurred in the placebo group, 2 occurred with celecoxib (annualised incidence 0.2%) and 9 occurred with conventional NSAIDs (1.68%, p=0.002). Nine cases occurred in the open-label study (annualised incidence 0.18%). The study concluded that the incidence of upper GI ulcer complications was 8-fold lower with celecoxib compared with conventional NSAIDs, and a similar rate to placebo [25].

Chan et al. assessed the effectiveness of celecoxib compared with diclofenac combined with omeprazole in 287 patients with RA and OA who presented with ulcer bleeding. The study found there to be no significant difference in the two treatments' effect on recurrent GI bleeding [24].

Other trials have reported either significantly lower [41,42] or comparable [40] rates of GI complaints with celecoxib [41, 42] compared with conventional NSAIDs.

Deeks Meta-Analysis

Deeks et al. report the finding of a systematic review and meta-analysis of RCTs comparing the efficacy, tolerability and upper gastrointestinal safety of celecoxib compared with conventional NSAIDs or placebo. They identified nine trials involving 15,172 patients with OA or RA. CLASS contributed to over half of the patients analysed.

The authors reported equivalent efficacy between celecoxib and conventional NSAIDs, but significantly greater tolerability in terms of withdrawals from the trials as a result of gastrointestinal complications including symptomatic ulcers, perforation, and haemorrhage. Deeks et al. reported that the RRR in serious GI events for patients administered celecoxib was 46% [28].

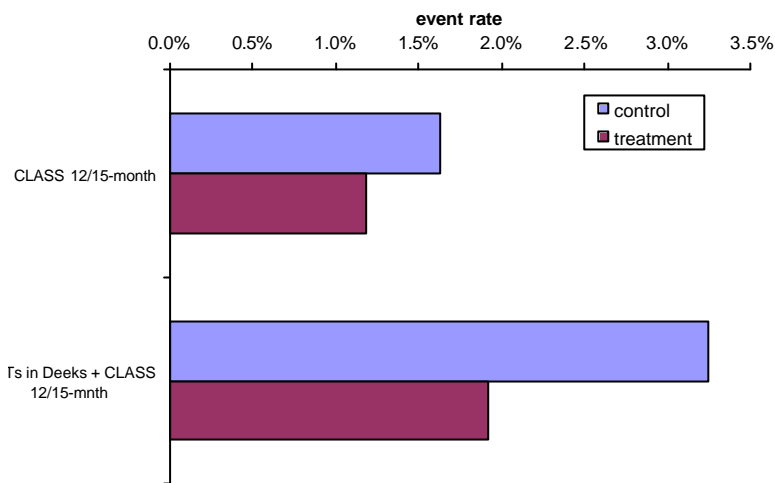
However, this meta-analysis has proved controversial, and a number of correspondents pointed out several errors (in total 19 rapid responses were accepted by the BMJ, see <http://bmj.com/cgi/eletters/325/7365/619>).

Questions were raised about the appropriateness of pooling of data from the two 6-month CLASS trials. Another criticism was the use of short-term trial results (only the CLASS trial was longer than 26 weeks) when patients generally take NSAIDs for many years [30]. The meta-analysis therefore does not provide us with any information on the long-term safety of celecoxib.

Perhaps most importantly, a number of authors pointed out that the meta-analysis did not use the 12-15 month CLASS data that were reported to the FDA [29, 30]. PHARMAC staff went on to apply the full CLASS data to the Deeks analysis, and found that these made a substantial difference to the GI safety profile of celecoxib [29].

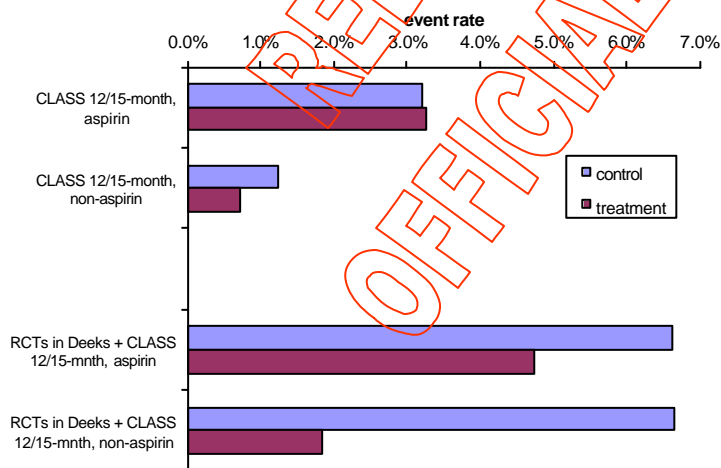
Combining the 12-month CLASS data with the seven trials in Deeks analysis, and then adjusting for the much longer exposure time experienced in CLASS, the overall RRR in serious GI events decreased to 32% (from 46% reported by Deeks). These results suggest that although celecoxib still causes statistically significant reductions in GI adverse events overall, reductions were appreciably less than suggested [29] (see Figure 1 below).

Figure 1. Withdrawals because of adverse GI effects in celecoxib vs. NSAID RCTs



Deeks et al also reported no statistically significant difference between low-dose aspirin and non-aspirin use for both endoscopic ulcers and for CLASS. PHARMAC however found that including the 12-15 month CLASS data gave a non-significant 28% RRR for aspirin use, compared with a 72% RRR for non-aspirin use – a statistically significant difference between RRRs. Adjusting for CLASS’ longer exposure gave again a non-significant 4% RRR for aspirin users, versus 52% for non-aspirin use, $p < 0.01$. Hence PHARMAC disagreed with any implication that celecoxib’s benefits extend equally to aspirin users [29] (see Figure 2 below).

Figure 2. Aspirin use in celecoxib vs. NSAID RCTs, for GDU + withdrawals from GI events: RCTs in Deeks + CLASS 12/15-month, exposure/variance-weighted



Further information on PHARMAC’s analysis (and Deeks et al. response) can be found on PHARMAC’s website:

www.pharmac.govt.nz/economic_analysis.asp.

Rofecoxib

VIGOR Trial

The VIGOR study demonstrated that rofecoxib was associated with a lower incidence of complicated ulcers compared to naproxen (0.4% compared with 0.9%, respectively) [35].

Laine et al. performed a post hoc analysis on serious lower and upper gastrointestinal events in the VIGOR trial. They found that serious lower GI events were 54% lower for patients administered rofecoxib compared with naproxen [43]. The number needed to treat with rofecoxib instead of naproxen to prevent one GI event was 10-12 in the highest risk patients (prior event, age ≥ 75 years, or severe rheumatoid arthritis), 17-33 in patients with other risk factors, and 42-106 in low-risk patients [44].

Other Trials

Hawkey et al. evaluated the effect of rofecoxib, ibuprofen, and placebo on the gastroduodenal mucosa of 775 patients with OA over a period of 24 weeks. The study found that ulcers were significantly less common in patients treated with rofecoxib [32]. Laine et al. reached similar conclusions in the trial of 742 OA patients randomised to received rofecoxib or isoprofen [7].

Appendix 4 – PTAC minutes

Included below are the amalgamated and summarised PTAC minutes on celecoxib and rofecoxib from the February 2000 to November 2001 PTAC meetings.

Celecoxib

PTAC considered an application for celecoxib in November 1999. Further information on celecoxib was considered in February 2000, May 2000, August 2000, and May 2001.

The committee considered that celecoxib appears to be similar in effectiveness and safety as other NSAIDs, but may have a better gastrointestinal safety profile. However, the latter issue has not been fully elucidated.

The committee noted there have been numerous reports suggesting an interaction between warfarin and celecoxib. The committee noted that an increased risk of bleeding for some patients on therapy with celecoxib and warfarin would preclude the funding of celecoxib for this subgroup on safety grounds.

As with other NSAIDs, the post-marketing surveillance (PMS) data suggest that the elderly, diabetics, patients with prior renal disease, and concomitant ACE inhibitor/diuretic use are risk factors for acute renal failure.

The committee noted that dyspepsia is a common side effect of celecoxib, which may lead to significant concomitant PPI use. The committee also noted that some patients would be on treatment with aspirin for coronary or cerebrovascular disease, and therefore already on treatment with PPI, which would make the benefit of using celecoxib instead of a NSAID questionable and the cost of treatment significantly greater.

PTAC considered celecoxib to be extremely expensive and agreed that the additional expenditure over NSAIDs would not be justified considering the modest decrease in serious gastrointestinal complications. In addition, patients at high risk of adverse events, including gastro-intestinal ones, would still have to be considered at high risk if treated with celecoxib and that, for this reason, PTAC could not recommend targeting to any specific sub-groups of patients. The committee considered that the place in therapy and safety profile of celecoxib still needs to be fully elucidated from post-marketing experience.

The committee, therefore, considered that the maximum benefit of celecoxib would only be achieved if the drug was made available to all patients requiring treatment with NSAIDs. The committee therefore supported the listing of celecoxib alongside NSAIDs and considered that this should be given a moderate priority.

Rofecoxib

PTAC considered an application in November 2000 to list rofecoxib 12.5 mg and 25 mg tablets on the Pharmaceutical Schedule. Further information was considered by PTAC in November 2001.

PTAC noted that rofecoxib is a selective COX-2 inhibitor that does not have a sulphonamide structure. The committee considered that the efficacy of rofecoxib was comparable with other conventional NSAIDs. The committee considered that rofecoxib had a superior gastrointestinal (GI) safety profile when compared with conventional NSAIDs. However, as with celecoxib, it considered that the true safety profile, particularly in elderly patients at high risk, would only become apparent after considerable post-marketing experience.

The committee noted the new evidence relating to the potential prothrombotic effects of rofecoxib shown in the VIGOR study. The committee considered that this could have been due to a positive effect of naproxen rather than a negative effect of rofecoxib.

The committee considered that concomitant use of low dose aspirin (to provide an anti-platelet effect) is likely to be routine in high risk cardiac patients and this will reduce the GI safety advantages of rofecoxib. Similarly, an increase in cardiovascular risk associated with rofecoxib in patients not on aspirin will also offset the safety advantages. The committee considered that patients with a high risk of developing upper GI perforations, ulcers and bleeding (PUBs), who are prescribed Vioxx, might still be prescribed a PPI.

The committee considered that the cost offsets in terms of reduction in the use of PPIs in patients with gastrotoxicity induced by conventional NSAIDs might not necessarily be high after they switched to rofecoxib. The committee noted that despite the lack of comparative data there was good evidence suggesting that a combination of PPI with a conventional NSAID protects against further PUBs, and could be used as an alternative approach.

The committee considered that patients at high risk of adverse events, including gastro-intestinal ones, would still be at risk if treated with rofecoxib and that, for this reason, it could not recommend targeting to any specific sub-groups of patients. The committee also considered the price of rofecoxib was disproportionately high compared to its potential benefits. The committee considered there to be no clinical reason not to list rofecoxib on the Pharmaceutical Schedule should an acceptable commercial arrangement be reached between the supplier and PHARMAC.

Appendix 5 – Other Cost/QALYs

Table 5: Comparison of Cost/QALY with other Economic Evaluations for Hospital Pharmaceuticals

Pharmaceutical	Year	Indication(s) Assessed	Marginal \$/QALY
Infliximab*	2002	Crohns disease	Single dose: \$53,000 Retreatment: \$118,000 Maintenance: \$382,000
Zoledronic acid*	2003	Hypercalcemia of malignancy (HCM); Bone metastases in breast cancer and multiple myeloma; Osteoporosis	HCM: \$20,000-\$40,000 Bone metastases: \$800,000
Linezolid*	2003	Methicillin-resistant <i>staphylococcus aureus</i> infections	Additional cost of \$1,300
Drotrecogin alfa (activated)*	2003	Severe sepsis	High risk of death: \$35,000 All patients: \$97,000 Low risk of death: less effective and more costly
Naltrexone	2003	Alcohol addiction	\$3,000
Venlafaxine	2003	Refractory depression	\$10,000-\$23,000 (depending on response to treatment)
Etanercept	2003	Rheumatoid arthritis	\$56,000 - \$62,000 (depending on length of use of cyclosporin)
Rituximab	2003	CD20 positive diffuse large B-cell NHL (stage II and above) in combination with CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone) chemotherapy	\$33,000 - \$46,000
Gabapentin*	2002	Last-line treatment for neuropathic pain	\$3,000-\$5,000
Imatinib mesylate*#	2002	Blastic and accelerated phases of Chronic Myeloid Leukemia (CML); Chronic phase after failure of interferon	Blastic phase: \$35,000-\$51,000 Accelerated phase: \$100,000 Chronic phase: \$110,000
Quetiapine*	2001	Schizophrenia	\$20,000
Enoxaparin	2001	Venous thromboembolism	Cost-saving
Tacrolimus*	1998	Renal transplantation	Renal Rescue: \$2,500 Primary: \$3,000-\$22,000 (depending on dose)

* Analyses available for DHBs to download from HPAD: www.pharmac.govt.nz/hpad/

The decision by PHARMAC to fund imatinib mesylate (Glivec) was not based on its cost-effectiveness alone. Rather, PHARMAC was able to negotiate cost-savings from a bundle of pharmaceuticals that made the funding of Glivec relatively cost-neutral.