PUBLIC SUMMARY DOCUMENT
Product: LUMIRACOXIB, tablet, 200 mg, Prexige®
Sponsor: Novartis Pharmaceuticals Australia Pty Ltd
Date of PBAC Consideration: November 2005

1. Purpose of Application

This submission sought a restricted benefit listing of lumiracoxib for the symptomatic treatment of osteoarthritis.

2. Background

At the November 2004 meeting, the PBAC rejected an application for a restricted benefit listing for symptomatic treatment of osteoarthritis on a cost-effectiveness basis because of insufficient evidence to demonstrate superiority in terms of gastrointestinal adverse effects, perforation, obstruction or bleeding (POBs) over celecoxib in order to justify any price advantage over celecoxib.

However, the PBAC also expressed concerns about the trend to increased risk of cardiovascular (CV) adverse effects over traditional NSAIDs, particularly in the light of similar concerns with the withdrawn rofecoxib. In this context, the PBAC also noted the request by the Adverse Reaction Advisory Committee (ADRAC) that the PBAC take into account ADRAC's reservations about the CV safety of the COX-2 inhibitors as a class. The PBAC therefore decided it would defer its consideration of whether to list lumiracoxib on a cost-minimisation basis compared with celecoxib, until the TGA completed its review of the CV safety of the COX-2 inhibitors.

3. Registration Status

Lumiracoxib is available in two strengths, 200 mg and 400 mg and is registered by the Therapeutic Goods Administration (TGA) for the following indications:

- symptomatic relief in the treatment of osteoarthritis;
- relief of acute pain, including post-operative pain and pain related to dental procedures;
- relief of pain due to primary dysmenorrhoea.

4. Listing Requested and PBAC's View

NOTE
The use of lumiracoxib for the treatment of the following conditions is not subsidised through the PBS:
(a) acute pain;
(b) soft tissue injury;
(c) arthrosis without an inflammatory component

Restricted benefit
Symptomatic treatment of osteoarthritis.
NOTE:
No applications for increased quantities or repeats will be authorised.

The PBAC noted that the restriction is identical to celecoxib and meloxicam restrictions for osteoarthritis. The PBAC also noted that a NOTE prohibiting approvals for increase maximum quantities was consistent with the approved PI statement "patients should not exceed this dose".

The PBAC also noted that listing was only sought for the 200 mg strength.

5. Clinical Place for the Proposed Therapy

Lumiracoxib 200 mg would provide an alternative treatment for patients with symptomatic osteoarthritis.

6. Comparator

The submission had nominated celecoxib as the appropriate comparator. The PBAC considered that this was appropriate.

7. Clinical Trials

The following data with respect to clinical trials, comparative effectiveness and comparative toxicity was provided to the November 2004 meeting:

- The primary efficacy analysis was based on three 13-week, head-to-head trials. Two compared lumiracoxib with celecoxib in osteoarthritis (OA) of the knee (Trials 0109 and 0112) and one compared lumiracoxib with rofecoxib in OA of the hip. (Trial 0128).
- Longer-term efficacy data were provided by a 39-week extension to Trial 0112 (Trial 0112E).
- The safety analysis was based on an indirect comparison between lumiracoxib, celecoxib and rofecoxib using traditional NSAIDs as a common comparator. A single trial each of lumiracoxib, celecoxib and rofecoxib (TARGET, CLASS and VIGOR respectively) were used to conduct the comparison. Whilst these trials had different endpoints (TARGET + CLASS: perforations, obstructions and bleeds (POBs); VIGOR: perforations, ulcers and bleeds (PUBs)) and were conducted in slightly different patient populations (TARGET: OA only; CLASS: OA and Rheumatoid arthritis (RA); VIGOR: RA only) at supratherapeutic doses, it was assumed that the event rates observed in these outcome studies are the upper limits of the events at recommended therapeutic doses.

Table 1: Trials included in the submission

Trial/first author	Citation	Publication Citation
Trial 0109	A13-week placebo-controlled trial assessing the safety and efficacy of lumiracoxib 200mg/day, lumiracoxib 400mg/day and celecoxib 200mg/day in patients with primary knee OA	
Trial 0112	A 13-week placebo-controlled trial assessing the safety and efficacy of lumiracoxib 200mg/day, lumiracoxib 400mg/day and celecoxib 200mg/day in patients with primary knee OA	
Trial 0128	A 13-week, placebo-controlled trial of lumiracoxib 400mg/day and rofecoxib 25mg/day in patients with primary OA in the hip	
Trial 0112E	A 39-week, uncontrolled extension to Trial 0112	
Schnitzer TJ,	Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), reduction in ulcer complications: randomised controlled trial.	Lancet 2004;364:665-74.
Farkouh ME et al	Comparison of lumiracoxib with naproxen and ibuprofen in the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), cardiovascular outcomes: randomised controlled trial	Lancet. 364(9435):675-84, 2004
Silverstein FE,	Gastrointestinal toxicity with celecoxib vs non-steroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis; the class study: a randomised controlled trial. Celecoxib longterm arthritis safety study. CLASS 2000	*JAMA* 2000; 284: 1247-1255.
Witter J.	FDA medical officer review of celecoxib. Medical Office Review [FDA] sNDA 20 998, 1-100. 2000. Center for Drug Evaluation and Research, FDA; 2000.	Available: http://www.fda.gov/cder/foi/nda/2002/20-998S009_Celebrex_medr_P1.pdf
Bombardier	Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR	N Engl J Med 2000;343:1520-1528.
Federal Drug Agency (FDA) advisory committee briefing document.	NDA 21-042 s007. VIOXX Gastrointestinal safety - Overall safety. February 2001.	Accesed from the FDA website http://www.fda.gov/
Goldkind L.	FDA Medical Officer's Advisory Committee GI Briefing Document. NDA 21-042 s007 and 21-052. June 2000.	Accessed from the FDA website [
Targum SI.	Review of cardiovascular safety database NDA 21-042 s007. FDA, 2001.	Accessed from the FDA website

8. Results of Trials

The PBAC (at the November 2004 meeting) agreed that lumiracoxib was shown to be as effective as celecoxib in treating the symptoms of osteoarthritis, noting that overall lumiracoxib 200 mg per day was not statistically different from celecoxib 200 mg per day for any of the primary outcomes: osteoarthritis, pain intensity, patients global assessment of disease activity; WOMAC pain subscale and WOMAC total score.

The general safety results from the 13-week head-to-head trials are summarised in the tables below:

Table 2: General safety results from the 13-week head-to-head trials

	Trial 0109		Trial 0112		Trial 0128	
	Lumiracoxib 200mg (N= 462)	**Celecoxib 200mg (N=444)**	**Lumiracoxib 200mg (N=487)**	**Celecoxib 200mg (N=481)**	**Lumiracoxib 400mg (N=205)**	**Rofecoxib 25mg (N=102)**
N° with AE	306 (66.2%)	298 (67.1%)	280 (57.5%)	256 (53.2%)	121 (59.0%)	56 (54.9%)
N° with SAE	32 [a] (7.0%) 7 (1.5%)	22 [a] (5.0%) 3 (0.7%)	22 [a] (4.5%) 12 (2.5%)	19 [a] (4.0%) 14 (2.9%)	10 [a] (5.0%) 4 (2.0%)	4 [a] (4.0%) 1 (1.0%)
Deaths	0	0	0	0	1 (0.5%)	0
N° with pre-specified AE	107 (23.2%)	84 (18.9%)	94 (19.3%)	77 (16.0%)	38 (18.5%)	21 (20.6%)
Pre-specified AE						
GI events (excluding ulcers)	96 (20.8%)	72 (16.2%)	84 (17.2%)	71 (14.8%)	35 (17.1%)	16 (15.7%)
GI ulcers	1 (0.2%)	0	1 (0.2%)	1 (0.2%)	0	0
GI events (including ulcers)	96 (20.8%)[d]	72 (16.2%)	85 (17.5%)	72 (15.0%)	35 (17.1%)	16 (15.7%)
Oedema	11 (2.4%)	12 (2.7%)	6 (1.2%)	6 (1.2%)	1 (0.5%)	4 (3.9%)
Chest pain	2 (0.4%)	4 (0.9%)	3 (0.6%)	2 (0.4%)	1 (0.5%)	0
CV events (excl chest pain)	2 (0.4%)	1 (0.2%)	NR	NR	3 (1.5%)	2 (2.0%)
Discontinuation due to:						
Any AE including SAEs	32 (6.9%)	33 (7.4%)	42 (8.6%)	47 (9.8%)	19 (9.3%)	10 (9.8%)
SAEs	3 (0.6%)	2 (0.5%)	8 (1.6%)	6 (1.2%)	3 (1.5%)	1 (1.0%)
AEs (non-serious)	29 (6.3%)	31 (7.0%)	35 (7.2%)	42 (8.7%)	16 (7.8%)	9 (8.8%)
Abnormal laboratory values	5 (1.1%)	2 (0.5%)	1 (0.2%)	0	3 (1.5%)	0

AE = adverse event, SAE = serious adverse event, CV = cardiovascular, NR = not reported
[a] Numbers calculated from percentages reported in the submission.
[d] One patient experienced both a GI ulcer and a GI event of constipation.

The incidence of adverse events in the short term head-to-head trials was similar for all treatment groups in all trials.

The following table summarises the safety data from the 39 week extension study:

Table 3: Safety data from the 39-week extension to Trial 0112 (0112E)

	Lumiracoxib 200mg/day (N=411)	**Celecoxib 200mg/day (N=405)**
Patients with AE	243 (59.1%)	222 (54.8%)
Patients with SAE	25 (6.1%)	20 (4.9%)
Deaths	0	1 (0.2%)
Total number with pre-specified AE	52 (12.7%)	50 (12.3%)
Pre-specified AEs		
GI events (excluding ulcers)	46 (11.2%)	39 (9.6%)
GI ulcers	0	2 (0.5%)

GI events (including ulcers)	46 (11.2%)	40 (9.9%)
Oedema	6 (1.5%)	6 (1.5%)
Chest pain	3 (0.7%)	4 (1.0%)
Discontinuation due to:		
Any AE including SAEs	48 (11.7%)	23 (5.7%)
SAEs	14 (3.4%)	4 (1.0%)
AEs (non-serious)	35 (8.5%)	20 (4.9%)

AE = adverse event, SAE = serious adverse event.

The following tables summarise safety results from the TARGET, CLASS and VIGOR trials. The data are sourced from the trials listed above and additional celecoxib data from the FDA website regarding results from the entire length of the planned CLASS study. These celecoxib data have not been published in the medical literature.

Table 4: Definite or probable upper GI complications (perforations, obstructions and bleeds - POBs)

	Treatment group	n/N (%)	N°/100 pat-yrs	K-M estimate	HR [a] (95% CI)	p-value	RR (95% CI)
TARGET							
Sub-study 0117	Lumiracoxib 400mg OD	19/4741 (0.40)	NR	0.50	0.37 (0.22, 0.63)	KM: 0.0001 HR: 0.0002	*0.38 (0.22, 0.64)* [b]
	Naproxen 500mg BD	50/4730 (1.06)	1.4	1.23			
Sub-study 2332	Lumiracoxib 400mg OD	10/4376 (0.23)	NR	0.28	0.29 (0.14, 0.59)	KM: 0.0003 HR: 0.0006	*0.30 (0.15, 0.62)* [b]
	Ibuprofen 800mg TDS	33/4397 (0.75)	1.2	0.94			
Total group	**Lumiracoxib 400mg OD**	**29/9117 (0.32)**	**NR**	**0.40**	**0.34 (0.22, 0.52)**	KM: <0.0001 HR: <0.0001	***0.35 (0.23, 0.53)*** [b]
	Traditional NSAIDs	**83/9127 (0.91)**	**NR**	**1.09**			
CLASS [c]							
	Celecoxib 400mg BD	17/3987 (0.43)	0.73	*0.68*	NR		
	Diclofenac 75mg BD	10/1996 (0.50)	0.93	NR	NR	0.640 [d,e]	*0.85 (0.39, 1.86)* [b]
	Ibuprofen 800mg TDS	11/1985 (0.55)	0.98	NR	NR	0.414 [d,f]	0.77 (0.36, 1.64)
Total group	**Celecoxib 400mg BD**	**17/3987 (0.43)**	**0.73**	***0.68***	**NR**	**0.450** [d]	**0.81 (0.43, 1.54)**
	Traditional NSAIDs	**21/3981 (0.53)**	**NR**	**NR**			
VIGOR							
	Rofecoxib 50mg OD	**16/4047 (0.40)**	**0.59**	**NR**	**NR**	**NR**	**0.43 (0.24, 0.78)** [g]
	Naproxen 500mg BD	**37/4029 (0.92)**	**1.37**	**NR**			

NR = not reported.
[a] Treatment comparisons using Cox proportional hazards model.
[b] *Calculated for the Commentary.*
[c] Data from entire study period.
[d] Log-rank p-value.
[e] Celecoxib versus diclofenac.
[f] Celecoxib versus ibuprofen.
[g] Of rofecoxib to naproxen from Cox model stratified by prior history of PUBs.

Table 5: Total Cardiovascular (CV) adverse events

	Treatment group	n/N (%)	N°/100 pat-yrs	K-M estimate	HR (95% CI)	p-value	RR (95% CI)

	Treatment group	n/N (%)	N°/100 pat-yrs	K-M estimate	HR (95% CI)	p-value	RR (95% CI)
TARGET [a]							
Sub-study 0117	Lumiracoxib 400mg OD	40/4741 (0.84)	NR	*1.05*	1.46 (0.89, 2.37)	KM: 0.1205 HR: 0.1313	*1.48 (0.91, 2.40)* [b]
	Naproxen 500mg BD	27/4730 (0.57)	NR	*0.75*			
Sub-study 2332	Lumiracoxib 400mg OD	19/4376 (0.43)	NR	*0.58*	0.76 (0.41, 1.40)	KM: 0.4499 HR: 0.3775	*0.83 (0.45, 1.52)* [b]
	Ibuprofen 800mg TDS	23/4397 (0.52)	NR	*0.71*			
Total group	**Lumiracoxib 400mg OD**	**59/9117 (0.65)**	**NR**	***0.83***	**1.14 (0.78, 1.66)**	**KM: 0.4543 HR: 0.5074**	***1.18 (0.81, 1.72)*** [b]
	Traditional NSAIDs	**50/9127 (0.55)**	**NR**	***0.73***			
CLASS [c,d]							
	Celecoxib 400mg BD	*52/3987 (1.30)* [e]	NR	NR	NR	NR	
	Diclofenac 75mg BD	*28/1996 (1.40)* [e]	NR	NR	NR	NR	*0.93 (0.59, 1.47)* [b]
	Ibuprofen 800mg TDS	*21/1985 (1.06)* [e]	NR	NR	NR	NR	*1.23 (0.74, 2.04)* [b]
Total group	**Celecoxib 400mg BD**	***52/3987 (1.30)*** [e]	**NR**	**NR**	**NR**	**NR**	**1.1 (0.7, 1.6)**
	Traditional NSAIDs	***49/3981 (1.23)*** [e]	**NR**	**NR**			
VIGOR [a]							
	Rofecoxib 50mg OD	**35/4047 (0.86)**	**1.30**	**NR**	**NR**	**NR**	***1.94 (1.10, 3.41)*** [b]
	Naproxen 500mg BD	**18/4029 (0.45)**	**0.67**	**NR**			

[a] Defined as confirmed or probable APTC endpoint.
[b] *Calculated for the Commentary.*
[c] Data from entire study period.
[d] Includes myocardial infarction, myocardial ischaemia, unstable angina, cardiac arrest, sudden/unexplained death and other cardiac death.
[e] Source: Table 2, White et al (2002).

The celecoxib dose in CLASS (400 mg twice a day) and the lumiracoxib dose in TARGET (400 mg/day) are twice the upper recommended therapeutic doses of each medication for the treatment of OA.

The rate of POBs for traditional NSAIDs was low in CLASS (0.53% for ibuprofen 2400 mg/day and diclofenac 150 mg/day) compared with that observed in TARGET (0.91% for ibuprofen 2400 mg/day and naproxen 1000 mg/day) and VIGOR (0.92% for naproxen 1000 mg/day).

As shown in Table 4, celecoxib did not show a statistically significant advantage over traditional NSAIDs in terms of POBs (0.43% vs 0.53%, log rank p=0.450). The TARGET trial indicated a significant advantage of lumiracoxib over traditional NSAIDs (0.32% vs 0.91%, p<0.001), and as with celecoxib, the GI advantage of lumiracoxib diminished to the point of non-significance in patients concomitantly taking low-dose aspirin.

The cardiovascular (CV) adverse events from the TARGET study (Table 5) indicate a non-significant trend to an elevated level of risk of CV events for lumiracoxib compared to naproxen. However, the reverse was shown when lumiracoxib was compared to ibuprofen. TARGET included patients who had taken low-dose aspirin for 3 months before enrolment; 10-11% of patients had a history of vascular disease and were indicated aspirin for secondary

prevention, 2% of patients were classified as "high" CV risk and were requiring aspirin for primary prevention. The PBAC in November 2004 noted there were questions concerning the power of TARGET to measure CV events.

9. Clinical Claim

In the submission to the November 2004 PBAC meeting the Committee agreed that lumiracoxib had similar effectiveness to celecoxib in treating the symptoms of osteoarthritis. However, the Committee considered there was insufficient evidence to demonstrate superiority of lumiracoxib over celecoxib in terms of gastrointestinal adverse effects.

At the November 2005 meeting the sponsor accepted the PBAC's view that lumiracoxib was as effective as celecoxib in treating the symptoms of osteoarthritis.

10. Economic Analysis

In the submission to this meeting the sponsor sought listing on a cost-minimisation basis with the equi-effective doses being lumiracoxib 200mg daily = celecoxib 200 daily.

11. Estimated PBS Usage and Financial Implications

In the submission to the November 2004 PBAC meeting it was estimated that the likely number of packs dispensed/year would be up to > 200,000 in Year 4 of listing. The withdrawal of rofecoxib would have affected this forecast.

The November 2004 submission estimated that the financial cost/year to the PBS would less than $10 million in Year 4 of listing but this would have been affected by the withdrawal of rofecoxib.

12. Recommendation and Reasons

The PBAC recommended listing for the symptomatic treatment of osteoarthritis only, on a cost-minimisation basis compared to celecoxib with the equi-effective daily doses being lumiracoxib 200 mg and celecoxib 200 mg.

The PBAC was concerned about the widespread availability of a further COX-2 selective inhibitor in light of ongoing concerns regarding cardiovascular risks associated with this group of drugs. It was noted that, in registering lumiracoxib, the TGA reviewed data relating to 18,000 patients. These data did not demonstrate an increased cardiovascular risk for lumiracoxib as compared to traditional NSAIDs, for example ibuprofen and diclofenac. However the PBAC noted that lumiracoxib was more selective for the COX-2 enzyme than celecoxib, and this was of potential concern. The PBAC recommended that the sponsor be encouraged to undertake post marketing surveillance activities particularly in light of the fact that the TARGET trial presented in the submission only provided 12 months worth of follow-up data, and that some of the more substantial evidence demonstrating the cardiovascular risk associated this group of drugs only become evident after 18 months' duration of therapy and follow-up of patients exposed to other COX-2 agents.

The PBAC also noted that the issue of cardiovascular toxicity associated with the traditional NSAIDs and COX-2 inhibitors was still evolving and was not yet resolved. Although there has been an overall reduction in the use of the COX-2 inhibitors in particular, the Committee expressed concern that the potential existed for lumiracoxib to have a high uptake and for the

usage to return to the levels of COX-2 inhibitor use prior to the removal of rofecoxib from the market.

The PBAC considered that in the current climate of uncertainty, caution in prescribing lumiracoxib was warranted, as the fundamental basis of risk versus benefit for this group of drugs had changed from when the COX-2 inhibitors were originally listed on the PBS.

It was noted that the National Prescribing Service (NPS) has already undertaken prescriber educational activities in this area, and it was suggested that the NPS publish a RADAR article to provide potential prescribers with relevant up-to date data on the potential risks in terms of cardiovascular toxicity of lumiracoxib. The PBAC also noted that lumiracoxib was not registered for use in rheumatoid arthritis – a fact that should be included in any NPS material to assist in preventing leakage to this indication.

Recommendations:
LUMIRACOXIB, tablet, 200 mg

Restriction:	Restricted benefit Symptomatic treatment of osteoarthritis. NOTE: No applications for increased quantities or repeats will be authorised. NOTE: The use of lumiracoxib for the treatment of the following conditions is not subsidised through the PBS: (a) acute pain; (b) soft tissue injury; (c) arthrosis without an inflammatory component.
Maximum quantity:	30
Repeats:	3

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

Novartis supports the need for post-marketing surveillance of marketed drugs and had *a priori* designed and implemented a world-wide pharmacovigilance and monitoring plan for lumiracoxib. The Prexige Risk Management Plan was discussed with the TGA prior to the November 2005 PBAC meeting. As a standard condition of registration Novartis supplies 6 monthly safety update reports to the TGA.