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Cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs - etodolac, meloxicam, celecoxib, rofecoxib, valdecoxib, etoricoxib and lumiracoxib - for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation

Addendum Report

NOTE: PRE-PEER REVIEW VERSION

Produced by West Midlands Health Technology Assessment Collaboration

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This report is an **addendum**, to the main assessment report 'Cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory drugs - etodolac, meloxicam, celecoxib, rofecoxib, valdecoxib and etoricoxib - for osteoarthritis and rheumatoid arthritis: a systematic review and economic evaluation', July 2004. This report should be read in conjunction with the main assessment report.

This report contains three sections:

1. **Assessment of the clinical effectiveness of lumiracoxib.**

2. **Assessment of the cost effectiveness of lumiracoxib.**

3. **Comparison and critique of the cost effectiveness results from the assessment group (AGM) and industry models for COX-2 selective NSAIDs.**

MATERIAL COMMERCIAL IN CONFIDENCE HAS BEEN REMOVED

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EXECUTIVE SUMMARY

Number and quality of studies, and direction of evidence:

Lumiracoxib – 15 randomised controlled trials were included. Studies compared lumiracoxib to either placebo, non-selective NSAIDs or other COX-2 selective NSAIDs. Compared to non-selective NSAIDs (diclofenac, ibuprofen or naproxen), lumiracoxib appeared to be equally efficacious and of significantly superior GI tolerability. Lumiracoxib was associated with significantly fewer clinical GI events (RR: 0.47, 95%: 0.36 to 0.60) and complicated clinical GI events (RR: 0.34, 95%CI: 0.23 to 0.52) and a statistically non-significant change in clinical confirmed myocardial infarction risk (RR: 1.71, 95% CI: 0.86 to 3.37).

Subgroup analyses – Subgroup analysis is suggestive of a reduction in lumiracoxib benefit on POBs in aspirin users. The increase in risk of clinical-confirmed myocardial infarction with lumiracoxib appeared higher in non-aspirin users. Given the very small number of clinical events observed in the trials, these data need confirmation.

Direct COX-2 comparisons – 7 RCTs were included. The efficacy of lumiracoxib compared to celecoxib and rofecoxib appears to be dose-dependent. There is no significant difference between these COX-2 selective NSAIDs in terms of tolerability and safety based on short-term trials.

COX-2 versus non-selective NSAID combined with a gastroprotective agent– No trials were identified

Cost & cost effectiveness:
Review of previous economic analyses – No previously published economic analysis was identified. No company model was submitted.

The Assessment Group Model -
Data Sources - The main data sources for clinical parameters are the meta-analysis results from our systematic review. Where necessary, we have used other sources.

Results - The base case incremental costs per QALY results for the simpler model are as follows:

COX-2 NSAID	**Population and Comparator**		
	Patients: standard[1] Comparator: NSAID[3] only	**Patients: standard[1] Comparator: NSAID[3] + PPI**	**Patients: high risk[2] Comparator: NSAID[3] + PPI**
Lumiracoxib	£70,500	Dominated[4]	Dominated[4]

1: age 58, no specific high risk factors; 2: prior GI ulcer; 3: diclofenac; 4: comparator costs lower and effects higher than COX-2 selective NSAID;

Limitations of the calculations: As main assessment report.

Need for further research: As main assessment report.

Conclusions:
The cost effectiveness of lumiracoxib looks very unattractive compared to non-selective NSAIDs alone or in combination with a PPI. This applies both to standard patients and to ‘high-risk’ patients defined in terms of previous GI events.

Lumiracoxib's license indication and dose are summarised in the table below:

Table 1: Recommended and maximum daily dose for lumiracoxib

Drug	OA		RA	
	Recommended	Maximum	Recommended	Maximum
Lumiracoxib	100-200mg	200mg	Not licensed	Not licensed

Source: company submission

1 CLINICAL EFFECTIVENESS OF LUMIRACOXIB

1.1 Methods

Methods are as described in the main assessment report (Section 4.1).

1.2 Results

1.2.1 Quantity of research available

Fifteen trials met inclusion criteria: a detailed summary of their characteristics are shown in Appendix 1 and summarised in Table 2. Most trials lasted three months or less and only two trials lasted 6-months or longer. The median sample size of trials was 893 patients. A key study,The Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), randomised over 18,000 patients.

TARGET

TARGET was a double blind RCT of patients with OA who were randomised, in two identical sub-studies to receive supra-license dose lumiracoxib (400mg daily, n=9,156), naproxen (1g per day, n=4754) in study 0117 or ibuprofen (2.4g daily, n=4415) in study 2332. The trial was designed to test the hypothesis that lumiracoxib reduced the risk of serious UGI complications compared with non-selective NSAIDs. A secondary objective was to compare cardiovascular morbidity and mortality between agents. Patients were stratified by age and use of low dose aspirin. The original protocol for TARGET was amended and patients with RA were excluded [CiC removed – rationale for the removal of RA patients from the TARGET study].

1.2.2 Description of included trials

Patient characteristics

Most trials studied patients with OA (9 studies), usually of the hip or knee. The average age of patients across trials ranged from 50 to 65 yrs and 63% to 84% were female. Details of baseline risk characteristics such as *H. pylori* status or previous peptic ulcers were either not reported or not collected in many trials; but where reported patients were of functional class I to III, 0% to 7% had experienced a previous GI ulcer, 0% to 24% were taking low dose aspirin and over 57% needed NSAIDs long-term.

Study interventions
Twelve trials studied licensed doses of lumiracoxib (100 mg/day, n=3 & 200mg per day n=9) and thirteen trials supra-license doses of lumiracoxib (>200mg/day). Lumiracoxib was compared with placebo in ten studies and with non-selective NSAIDs in eight: naproxen 1 g daily (n=4), diclofenac 150mg daily (n=2), or ibuprofen 2.4 g daily (n=3). Seven studies compared lumiracoxib to a COX-2 selective NSAID: celecoxib 200mg or 400mg daily (n=5) or rofecoxib 25mg once daily (n=2).

1.2.3 Assessment of quality of included trials

Trials were of high quality as judged by the Jadad scale: median score 5. A detailed summary of scores is provided in Appendix 2. It was possible, because of access to full trial reports for most trials, to assess trial design in detail. The majority of trials were properly randomised (11/15) and described methods of concealment well (11/15). All trials were double blind, stated intention-to-treat analysis (often a modified ITT), and all reported small losses to follow up (<5%).

Table 2: Characteristics and quality of included lumiracoxib randomised controlled trials

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Lumiracoxib	Placebo	NSAID	Efficacy+	Safety+		
Schnitzer (2000) Novartis Study 0104, Multinational [1]	OA (hip or knee)	100mg per day (50mg bd) (n=98) 200mg per day (100mg bd) (n=96) 400mg per day (200mg bd) (n=99) 400mg per day (400mg od) (n=99)	n=97	Diclofenac 150mg per day (75mg bd) (n=94)	Pain (VAS), Patient's global assessment, [CiC removed]	Withdrawal due to adverse events, Total withdrawal, Ulcer (clinical or symptomatic), Dyspepsia, Myocardial infarction, Total cardiovascular thrombotic, Total AE severe, Total AE, Withdrawals due to GI AE]	4	4
Hawkey (2002) Novertis Study 0126, [CIC removed] 13 weeks treatment [2]	OA	200mg per day (200mg od) (n=264) 400mg per day (400mg od) (n=260)	-	Celecoxib 200mg per day (200mg od) (n=258) Ibuprofen 2400mg per day (800mg tds) (n=260)	[CiC removed]	Ulcer (endoscopic), [CIC removed]	13	5
Benevolenskaya (2003) Novartis Study 2316, [CIC removed] [3]	OA (knee or hip)	100mg per day (100mg od) (n=122)	n=122	-	Pain (VAS), Patient's global assessment, [CIC removed]	Total AE severe, Total AE [CiC removed]	4	5

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Lumiracoxib	Placebo	NSAID	Efficacy+	Safety+		
Fleischmann (2003) Novartis Study 0109, [CIC removed] [4]	OA (knee)	200mg per day (200mg od) (n=465) 400mg per day (400mg od) (n=465)	n=232	Celecoxib 200mg per day (200mg od) (n=446)	Pain (VAS), Patient's global assessment, [CIC removed]	Total AE severe, Total AE, [CIC removed]	13	5
Grifka (2003) Novartis Study 2319, [CIC removed] [5]	OA (hand)	200mg per day (200mg od) (n=205) 400mg per day (400mg od) (n=193)	n=196	-	Pain (VAS), Patient's global assessment, , [CIC removed]	Total AE severe, Total AE [CIC removed]	4	4
Tannenbaum (2004)[6] Novartis Study 0112 [CIC removed] multicentre	OA (knee)	200mg per day (200mg od) (n=487) 400mg per day (400mg od) (n=491)	n=243	Celecoxib 200mg per day (200mg od) (n=481)	Pain (VAS), Patient's global assessment, [CIC removed]	Total AE severe, Total AE [CIC removed]	13	5
Novartis Study 0128 [CiC removed]	[CiCremoved]	[CiCremoved]	[CiCremoved]	[CiCremoved]	[CiCremoved]	[CiCremoved]	[CiCremoved]	[CiCremoved]

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Lumiracoxib	Placebo	NSAID	Efficacy+	Safety+		
Novartis Study 2307 [CiCremoved]	[CiCremoved]	[CiCremoved]	[CiCremoved]	[CiCremoved]	[CiCremoved]	[CiCremoved]	[CiCremoved]	[CiCremoved]
TARGET, Novartis Study 0117+ A2332 Multinational [7-9]	OA (hip, knee, hand, cervical or lumbar spine)	400mg per day (400mg od) (n=9156)	-	Naproxen 1000mg per day (500mg bd) or Ibuprofen 2400mg per day (800mg tds) (n=9169)	Pain (Likert), Patient's global assessment, Withdrawal due to lack of efficacy	Total withdrawal, Ulcer (clinical/symptomatic), Total PUB, Dyspepsia, Myocardial infarction, Total cardiovascular thrombotic, Total AE severe, Total AE, Withdrawals due to GI AE	52	5
Guesens (2003) Novartis Study 0111, [CiC removed] [10]	RA	200mg per day (200mg od) (n=280) 400mg per day (400mg od) (n=281)	n=284	Naproxen 1000mg per day (500mg bd) (n=279)	Pain CIC Patient's global assessment, [CiCremoved]	[CiCremoved]	26	[CiC removed]
Kivitz (2004) Novartis Study 0110, Multinational [11]	RA	400mg per day (400mg od) (n=227) 800mg per day (800mg od) (n=227)	-	Celecoxib 400mg per day (200mg bd) (n=223) Ibuprofen 2400mg per day (800mg tds) (n=216)	Pain (Likert), Patient's global assessment, Withdrawal due to lack of efficacy	Total withdrawal, Ulcer (clinical/symptomatic), Dyspepsia, Myocardial infarction, Total cardiovascular thrombotic, Total AE severe, Total AE	13	4
Scott (2003) Novartis Study 2312, [CiC removed][12]	RA	800mg per day (800mg od) (n=CIC) 1200mg per day (1200mg od) (n=CIC)	-	Naproxen 1000mg per day (500mg bd) (n=CIC)	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]

Author year, trial name	RA/OA (location)	Drug, dose and no. randomised			Outcomes		Duration (weeks)	Jadad score
		Lumiracoxib	Placebo	NSAID	Efficacy+	Safety+		
Novartis Study 0105 [CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]
Novartis Study 0114, [CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]
Novartis Study A2335, [CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]	[CiC removed]

+Only the outcomes which were included in meta-analyses are listed.

1.2.4 Assessment of lumiracoxib efficacy

Efficacy results are summarised in Table 3 (placebo-only information in grey shaded cells).

Patient's assessment of arthritis pain
There was no statistically significant improvement in pain over non-selective NSAIDs. This was true for OA and RA patients, different doses of lumiracoxib and choice of comparator NSAID although the number of trials overall was small.

Patient's assessment of global efficacy
There was evidence of a greater improvement in global efficacy with non-selective NSAIDs compared to lumiracoxib. However, the number of reporting trials was small.

ACR-20 responder
ACR-20 was reported in only three trials of RA patients. Lumiracoxib was no better than comparator NSAIDs. This result appeared to be consistent for lumiracoxib dose and choice of comparator.

Withdrawals due to lack of efficacy
There was no difference in withdrawal rates on comparing lumiracoxib with non-selective NSAIDs. This was true for OA and RA patients, lumiracoxib dose and choice of NSAID comparator.

Table 3: Summary of efficacy results of lumiracoxib versus placebo and NSAIDs

	Placebo				NSAID			
	VAS Pain difference Mean (95% CI) **	**VAS Global efficacy difference Mean (95% CI)****	**ACR 20 RR (95% CI)**	**Withdrawals due to lack of efficacy RR (95% CI)**	**VAS Pain difference Mean (95% CI)****	**VAS Global efficacy difference Mean (95% CI)****	**ACR 20 RR (95% CI)**	**Withdrawals due to lack of efficacy RR (95% CI)**
100mg/day	*-7.20 (-10.65 to -3.75) [3]*	*-8.57 (-12.18 to -4.97)[3]*	CiC [1]	*0.20 (0.06 to 0.62) [3]*	1.07 (-3.10 to 5.25) [2]	2.78 (-1.60 to 7.16) [2]	CiC [1]	2.88 (0.12 to 69.80) [1] †
200mg/day	*-6.32 (-7.83 to -4.80) [8]*	*-6.69 (-8.24 to -5.14) [8]*	*1.24 (1.12 to 1.37) [4]*	*0.59 (0.51 to 0.68) [8]*	1.77 (-1.89 to 5.44)* [4]	*2.57 (0.16 to 4.98) [4]*	0.97 (0.86 to 1.10) [3]	*1.48 (1.13 to 1.94) [5]*
>200mg/day	*-7.52 (-9.10 to -5.95) [8]*	*-8.54 (-10.81 to -6.27)* [8]*	*1.18 (1.03 to 1.35) [3]*	*0.55 (0.46 to 0.65) [8]*	-0.18 (-2.91 to 2.55) [3]	0.51 (-2.36 to 3.38) [3]	0.98 (0.81 to 1.18) [2]	1.03 (0.94 to 1.13) [7]
OA only	*-8.11 (-9.80 to -6.42) [6]*	*-9.24 (-11.00 to -7.48) [6]*	No trials	*0.44 (0.34 to 0.59) [6]*	-0.02 (-4.23 to 4.19) [1]	2.01 (-2.54 to 6.56) [1]	No trials	1.03 (0.93 to 1.13) [3]
RA only	*-5.46 (-7.36 to -3.57) [4]*	*-5.24 (-7.16 to -3.31) [4]*	*1.22 (1.11 to 1.34) [4]*	*0.61 (0.53 to 0.69) [4]*	1.71 (-2.24 to 5.67)* [3]	2.13 (-1.88 to 6.14)* [3]	0.96 (0.86 to 1.08) [3]	1.23 (0.74 to 2.03)* [5]
All trials	*-6.94 (-8.20 to -5.67) [10]*	*-7.51 (-9.27 to -5.76)* [10]*	*1.22 (1.11 to 1.34) [4]*	*0.53 (0.44 to 0.65) [10]*	1.13 (-0.93 to 3.18) [4]	*2.25 (0.14 to 4.37) [4]*	0.96 (0.86 to 1.08) [3]	1.13 (0.85 to 1.50) [8]

* heterogeneity P<0.10 & random effects model used; [ ]: N trials; † one trial reported zero events in both arms; **: assessed using 100mm VAS scale.

1.2.5 Lumiracoxib tolerability

Adverse events

Adverse events are separated into two categories: all adverse events and GI-related adverse events (see Table 4). Both overall and GI-specific adverse events were reduced with lumaricoxib compared to non-selective NSAIDs. There was evidence of significant statistical heterogeneity across trials. These results appeared to be consistent across type of arthritis and dose of lumiracoxib.

Withdrawals

Withdrawals are considered at three levels: withdrawal from the trials from any reason (including loss to follow up, lack of efficacy or adverse events), withdrawal due to adverse events, and withdrawal due to GI-specific adverse events (see Table 5). The proportion of withdrawal due to all adverse event and GI-specific adverse events with lumiracoxib was lower than non-selective NSAIDs. There was no significant difference in withdrawals for any reason. There was evidence of statistical heterogeneity across all withdrawal outcomes. Results appeared to be consistent across dose of lumiracoxib and type of arthritis.

Table 4: Summary of adverse events for lumiracoxib versus placebo & NSAIDs

	Placebo **Relative risk (95% CI)** **[N trials]**	**NSAIDs** **Relative risk (95% CI)** **[N trials]**
All adverse events		
100mg per day	1.07 (0.85 to 1.34) [2]	CiC [1]
200mg per day	*1.07 (1.00 to 1.14) [7]*	*0.91 (0.85 to 0.99) [4]*
>200mg per day	1.05 (0.98 to 1.12) [7]	0.95 (0.89 to 1.01)* [6]
OA only	1.06 (0.98 to 1.14) [5]	0.99 (0.98 to 1.01) [2]
RA only	1.07 (0.99 to 1.16) [4]	*0.91 (0.86 to 0.98) [5]*
All trials	*1.07 (1.01 to 1.13) [9]*	*0.94 (0.89 to 1.00)* [7]*
All GI adverse events		
100mg per day	1.12 (0.62 to 2.03)* [3]	*0.51 (0.37 to 0.69) [2]*
200mg per day	*1.30 (1.13 to 1.50) [8]*	*0.69 (0.53 to 0.90)* [5]*
>200mg per day	*1.41 (1.22 to 1.62) [8]*	*0.84 (0.75 to 0.94)* [7]*
OA only	*1.47 (1.24 to 1.74) [6]*	*0.84 (0.72 to 0.99)* [3]*
RA only	*1.20 (1.01 to 1.43) [4]*	*0.75 (0.59 to 0.95)* [5]*
All trials	*1.34 (1.19 to 1.51) [10]*	*0.79 (0.70 to 0.90)* [8]*

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

Table 5: Summary of withdrawals for lumiracoxib versus placebo & NSAIDs

	Placebo Relative risk (95% CI) [N trials]	**NSAIDs Relative risk (95% CI) [N trials]**
All adverse event withdrawals		
100mg per day	0.86 (0.43 to 1.71) [3]	*0.39 (0.21 to 0.75) [2]*
200mg per day	1.04 (0.82 to 1.31) [8]	*0.60 (0.45 to 0.80) [5]*
>200mg per day	1.15 (0.92 to 1.44) [8]	*0.65 (0.46 to 0.90)* [7]*
OA only	1.05 (0.80 to 1.37) [6]	0.51 (0.26 to 1.02)* [3]
RA only	1.16 (0.88 to 1.53) [4]	*0.74 (0.58 to 0.95) [5]*
All trials	1.10 (0.91 to 1.34) [10]	*0.64 (0.48 to 0.86)* [8]*
All GI withdrawals		
100mg per day	0.98 (0.25 to 3.84) [2]	CiC [1]
200mg per day	1.29 (0.78 to 2.12) [5]	*0.39 (0.23 to 0.66) [3]*
>200mg per day	1.59 (0.97 to 2.60) [5]	*0.70 (0.64 to 0.77) [4]*
OA only	1.57 (0.92 to 2.69) [4]	*0.60 (0.39 to 0.94)* [2]*
RA only	1.16 (0.59 to 2.28) [3]	*0.35 (0.18 to 0.69) [3]*
All trials	1.41 (0.92 to 2.14) [7]	*0.50 (0.32 to 0.79)* [5]*
All withdrawals		
100mg per day	0.65 (0.41 to 1.02) [3]	0.60 (0.36 to 1.01) [2]
200mg per day	*0.75 (0.68 to 0.82) [8]*	0.85 (0.57 to 1.27)* [5]
>200mg per day	*0.81 (0.73 to 0.91) [8]*	0.83 (0.68 to 1.01)* [7]
OA only	*0.79 (0.68 to 0.92) [6]*	0.70 (0.47 to 1.05)* [3]
RA only	*0.75 (0.68 to 0.83) [4]*	1.02 (0.73 to 1.42)* [5]
All trials	*0.77 (0.70 to 0.83) [10]*	0.88 (0.72 to 1.07)* [8]

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis

1.2.6 Lumiracoxib safety

The safety of lumiracoxib was evaluated by considering the development of endoscopic GI ulcers, clinical UGI events (PUBs), complicated UGI event (POBs), clinical myocardial infarctions and serious cardiovascular thrombotic events (see Table 7).

Endoscopic ulcers

In the two trials that reported endoscopic ulcers, there was a statistically significant reduction in ulcers with lumiracoxib compared to non-selective NSAIDs. There is insufficient evidence to comment on the effect of lumiracoxib dose and type of arthritis on endoscopic ulcers.

Clinical UGI events (PUBs)

In one of the two trials that reported PUBs, there was a statistically significant reduction in PUBs with lumiracoxib compared to non-selective NSAIDs. [Results of CIC study removed]. There is insufficient evidence to comment on the effect of lumiracoxib dose and type of arthritis. Virtually all events come from TARGET, which included only OA patients. See Figure 1.

Complicated UGI events (POBs)
In one of the two trials that reported POBs there was a statistically significant reduction in ulcers with lumiracoxib compared to non-selective NSAIDs. [Results of CIC study removed]. There is insufficient evidence to comment on the effect of lumiracoxib dose and type of arthritis. Again, virtually all events come from TARGET..See Figure 2.

Myocardial infarctions and serious cardiovascular thrombotic events
In the trials that reported myocardial infarction, there was an increase in the number of clinical events with lumiracoxib compared to non-selective NSAIDs although this failed to reach statistical significance. There was no significant difference in cardiovascular thrombotic events on comparing lumiracoxib and non-selective NSAIDs. There is insufficient evidence to comment on the effect of different lumiracoxib doses and types of arthritis. As before, the majority events come from TARGET.See Figure 3.

Table 6: Summary of endoscopic GI ulcers and serious GI events (PUBs and POBs) for lumiracoxib versus placebo & NSAIDs

	Placebo **Relative risk (95% CI) [N trials]**	**NSAID** **Relative risk (95% CI) [N trials]**
Endoscopic GI ulcers		
100mg per day	No trials	No trials
200mg per day	No trials	*0.27 (0.14 to 0.52) [1]*
>200mg per day	No trials	*0.26 (0.16 to 0.41) [2]*
OA only	No trials	*0.26 (0.16 to 0.44) [1]*
RA only	No trials	*[0.26 (0.14 to 0.48) [1]*
All trials	No trials	*0.26 (0.18 to 0.39) [2]*
POBs		
100mg per day	¶	[CiC removed] [1]
200mg per day	[CiC removed] [1][a]	[CiC removed] [1][e]
>200mg per day	1.99 (0.22 to 17.78) [2][b]	*0.35 (0.23 to 0.52) [2][e]*
OA only	1.25 (0.15 to 10.67) [2][c]	*0.35 (0.23 to 0.53) [1]*
RA only	[c]	[CiC removed] [1] ¶
All trials	1.25 (0.15 to 10.67) [2][d]	*0.34 (0.23 to 0.52) [2]* ¶
PUBs		
100mg per day	¶	[CiC removed] [1]
200mg per day	0.89 (0.16 to 5.04) [3][c]	[CiC removed] [1][e]
>200mg per day	2.26 (0.37 to 13.64) [3][c]	*0.47 (0.36 to 0.60) [2][e]*
OA only	1.50 (0.18 to 12.43) [2][c]	*0.47 (0.37 to 0.61) [1]*
RA only	0.69 (0.08 to 5.75) [2][e]	[CiC removed] [1] ¶
All trials	1.04 (0.24 to 4.51) [4][b]	*0.47 (0.36 to 0.60 [2]* ¶

¶ two trials reported zero events in both arms. [a] five trials reported zero events in both arms. [b] four trials reported zero events in both arms. [c] three trials reported zero events in both arms. [d] six trials reported zero events in both arms. [e] one trial reported zero events in both arms.

Figure 1: Risk of PUBs with lumiracoxib (all doses) vs NSAIDs (all drugs) [figure CIC except pooled estimate, which is reported in table]

Figure 2: Risk of POBs with lumiracoxib (all doses) vs NSAIDs (all drugs) [figure CIC except pooled estimate, which is reported in table]

Table 7: Summary of serious CV events for lumiracoxib versus placebo & NSAIDs

	Placebo **Relative risk (95% CI) [N trials]**	**NSAID** **Relative risk (95% CI) [N trials]**
MI		
100mg per day	¶	[c]
200mg per day	3.03 (0.37 to 25.13) [2][a]	[CiC removed]) [1][c]
>200mg per day	2.13 (0.23 to 19.74) [2][a]	1.66 (0.83 to 3.34) [2][c]
OA only	1.28 (0.22 to 7.43) [3] ¶	1.67 (0.82 to 3.41) [1]
RA only	[CiC removed]) 1] ¶	2.04 (0.23 to 18.15) [2][c]
All trials	2.01 (0.47 to 8.67) [4][a]	1.71 (0.86 to 3.37) [3][c]
Serious CV thrombotic events		
100mg per day	¶	[c]
200mg per day	2.47 (0.43 to 14.13) [3][b]	[CiC removed]) [1][c]
>200mg per day	1.59 (0.21 to 11.80) [2][a]	1.19 (0.82 to 1.72) [2][c]
OA only	1.15 (0.21 to 6.26) [3] ¶	1.18 (0.81 to 1.72) [1]
RA only	[CiC removed]) [1] ¶	1.19 (0.18 to 7.95) [2][c]
All trials	1.78 (0.44 to 7.27) [4][a]	1.18 (0.82 to 1.71) [3][c]

*Significant (P<0.10) statistical heterogeneity – random effects meta-analysis. ¶ two trials reported zero events in both arms. [a] four trials reported zero events in both arms. [b] three trials reported zero events in both arms. [c] one trial reported zero events in both arms

Figure 3: Risk of MI with lumiracoxib (all doses) vs NSAIDs (all drugs) [figure CIC except pooled estimate, which is reported in table]

[CiC figure removed]

1.2.7 Subgroup analyses

Stratified analyses of endoscopic ulcers according to *H. Pylori* status was reported in trial 0110; and TARGET reported subgroup analyses of POBs and MIs by low dose aspirin use. None of the identified trials reported subgroup analyses for age, prior GI status, steroid or anti-coagulant use.

Endoscopic ulcers

Stratified pooled relative risks for endoscopically-detected ulcers with lumiracoxib compared to conventional NSAIDs are summarised in Table 8.

Table 8: Endoscopic ulcer for lumiracoxib vs non-selective NSAID by sub-groups

Subgroup [N trials]	**Pooled events Lumiracoxib vs NSAID**	**Relative risk (95% CI)****	**P-value+**
H-pylori status			
Positive [1]	8/179 vs 14/91	0.29 (0.13 to 0.67)	0.65
Negative [1]	6/219 vs 12/96	0.20 (0.08 to 0.51)	

**Relative risk lumiracoxib vs non-selective NSAID
+Chi-square test of heterogeneity

There are few events in these subgroups and results should be interpreted with caution. Lumiracoxib significantly reduced endoscopic events compared to non-selective NSAIDs in each subgroup pair.

POBs

The subgroup analyses for aspirin users from the TARGET trial are summarised in Table 9.

Table 9: POBs for lumiracoxib vs non-selective NSAID by low dose aspirin use

Subgroup [N trials]	**Pooled events**	**Pooled relative risk (95% CI)****	**P-value+**
POBs			
User [1]	15/2167 vs 19/2159	0.78 (0.40 to 1.54)	0.005
Non user [1]	14/6950 vs 64/6968	0.22 (0.12 to 0.40)	

**Relative risk lumiracoxib vs non-seective NSAID
+Chi-square test of heterogeneity

Analysis suggests that lumaricoxib is less beneficial, in terms of POBs, in aspirin users. However, given the very small number of events observed, these data need confirmation. TARGET reported a significant reduction in POBs with lumiracoxib compared with non-selective NSAID regardless of *H Pylori* status, although the numbers were not reported.

Myocardial infarction

Subgroup analysis for low dose aspirin on MI (clinically confirmed) rates from the TARGET trial are summarised in

Table 10: MI for celecoxib vs conventional NSAID by low dose aspirin use

Subgroup [N trials]	Pooled events	Pooled relative risk (95% CI)**	P-value+
MI			
User [1]	6/2167 vs 7/2159	1.37 (0.53 to 3.57)	0.118
Non user [1]	14/6950 vs 5/6968	4.51 (1.43 to 14.22)	

**Relative risk lumiracoxib vs conventional NSAID
+Chi-square test of heterogeneity

The increase in risk of clinically confirmed MI with lumiracoxib compared to non-selective NSAIDs appeared higher in non-aspirin users than aspirin users. Given the relatively small number of events, caution is necessary when interpreting these data.

1.2.8 Impact of concomitant gastroprotective agents

No relevant trials identified.

1.2.9 Direct comparison of lumiracoxib to other COX-2 selective NSAIDs

Description of included trials, patient characteristics and trial quality

Seven trials compared lumiracoxib with another COX-2 selective NSAID: five with celecoxib and two with rofecoxib. All, but one, trials were of 13 weeks duration. Two trials compared lumiracoxib 200 to 800 mg per day to celecoxib 400 mg per day in RA patients. The remaining trials compared lumiracoxib 200 to 400 mg per day to either celecoxib 200 mg per day or rofecoxib 25 mg per day in OA patients. Two of the trials also had ibuprofen arm and four had placebo arms. The results of these comparisons were reported in the previous section. Full details of the trials are listed in Appendix 1 and are summarised in Table 2.

Sample sizes of the trials ranged from 309 to 1702 (median 1042). The trials were of good quality. Six trials scored 5 on the Jadad scale and one scored 4 due to lack of reporting of randomisation method.

Efficacy

Patient's assessment of arthritis pain

Substantial heterogeneity exists between the three trials which compared lumiracoxib with celecoxib and reported VAS pain (see Figure 4). There were no significant differences between lumiracoxib 200 – 400 mg per day and celecoxib 200 mg per day in OA patients (Fleischmann 2003, Tannenbaum 2004). [CiC text removed – results of study 0114 and 0128]

Patient's assessment of global efficacy
The results of patient's assessment of global efficacy mirrored the results for pain: lumiracoxib was equally efficacious to celecoxib 200 mg per day in OA patients, but was less efficacious than celeoxib 400 mg per day in RA patients (see Figure 5). [CiC text removed – results of study 0128]

ACR-20 responder
[CiC removed – results of study 0114]

Withdrawal due to lack of efficacy
Overall there was no significant difference in withdrawals due to lack of efficacy between lumiracoxib and celecoxib. [CiC removed – results of study 0114]. There was no difference between lumiracoxib 400 mg per day and rofecoxib 25 mg per day in OA (Figure 7).

Efficacy results and comparisons with celocoxib and rofecoxib are summarised in Appendix 3.

Figure 4: Comparison of change in VAS pain between lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled estimate]

[CiC figure removed Overall WMD=0.26 95% CI: -3.45, 3.98]

Figure 5: Comparison of change in patient's global assessment (VAS) between lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled esitmate

[CiC figure removed- Overall WMD= 0.53; 95% CI: -2.83, 3.89]

Figure 6: Comparison of level of withdrawal due to lack of efficacy in lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled estimate]

[CiC figure removed- Overall RISK RATIO 1.12; 95% CI: 0.89, 1.40]

Figure 7: Comparison of level of withdrawal due to lack of efficacy in lumiracoxib 400mg/day and rofecoxib 25mg/day [figure CIC except pooled estimate]

[CiC figure removed- Overall Risk Ratio 0.87 95% CI: 0.37, 2.04]

Tolerability

Total adverse events
There were no significant differences in total adverse events between lumiracoxib and celecoxib, and between lumiracoxib and rofecoxib (see Figure 8 and Figure 9).

GI adverse events
No significant differences were observed in GI adverse events between lumiracoxib and celecoxib, and between lumiracoxib and rofecoxib, although the pooled estimates showed slight trends in favour of celecoxib and rofecoxib (see Figure 10 and Figure 11).

Withdrawals due to adverse events
There were no significant differences in withdrawal due to adverse events between lumiracoxib and celecoxib, and between lumiracoxib and rofecoxib (see Figure 12 and Figure 13).

Withdrawals due to GI events
No significant differences in withdrawal due to GI adverse events were found between lumiracoxib and celecoxib, and between lumiracoxib and rofecoxib (see Figure 14 and Figure 15).

Total withdrawal
Overall, withdrawals for any reason were similar between lumiracoxib treatment groups and celecoxib or rofecoxib groups. Nevertheless, Kivitz and colleagues reported significantly more withdrawals for any reason in lumiracoxib 400 – 800 arms than in celecoxib 400 mg arm (see Figure 16 and Figure 17).

Figure 8: Comparison of overall adverse events with lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled estimate]

[CiC figure removed- Overall Risk Ratio1.01; 95% CI: 0.96, 1.05

Figure 9: Comparison of overall adverse events with lumiracoxib (400mg/day) and rofecoxib (25mg/day) [figure CIC except pooled estimate]

[CiC figure removed-Overall Risk Ratio 1.06 95% CI: 0.94, 1.21]]

Figure 10: Comparison of GI adverse events with lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled estimate

[CiC figure removed- Overall Risk Ratio 1.09 95% CI: 0.99, 1.18]

Figure 11: Comparison of GI adverse events with lumiracoxib (400mg/day) and rofecoxib (25mg/day) [figure CIC except pooled estimate]

[CiC figure removed- Overall Risk Ratio 1.17 95% CI: 0.94, 1.46]

Figure 12: Comparison of withdrawals due to adverse events with lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled estimate]

[CiC figure removed- Overall Risk Ratio 0.96 95% CI: 0.79, 1.17]

Figure 13: Comparison of withdrawals due to adverse events with lumiracoxib (400mg/day) and rofecoxib (25mg/day) [figure CIC except pooled estimate]

[CiC figure removed- Overall Risk Ratio 1.11 95% CI: 0.63, 1.98]

Figure 14: Comparison of withdrawals due to GI adverse events with lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled estimate]

[CiC figure removed- Overall Risk Ratio 1.01 95% CI: 0.73, 1.39]

Figure 15: Comparison of withdrawals due to GI adverse events with lumiracoxib (400mg/day) and rofecoxib (25mg/day) [figure CIC except pooled estimate]

[CiC figure removed- Overall Risk Ratio 0.88 95% CI: 0.42, 1.84]

Figure 16: Comparison of overall withdrawals with lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled estimate]

[CiC figure removed- Overall Risk Ratio 1.09 95% CI: 0.97, 1.22]

Figure 17: Comparison of overall withdrawals with lumiracoxib (400mg/day) and rofecoxib (25mg/day) [figure CIC except pooled estimate]

[CiC figure removed- Overall Risk Ratio 1.11 95% CI: 0.74, 1.66]

Safety

Endoscopic GI ulcers
Two trials reported no significant difference in endoscopically detected ulcers between lumiracoxib and celecoxib treatment arms. (see Figure 18) No trial which compared lumiracoxib and rofecoxib reported this outcome.

Clinical UGI events (PUBs) and complicated UGI events (POBs)
Three trials comparing lumiracoxib to celecoxib reported a total of five POBs and nine PUBs (see Figure 19 and Figure 20). There were no significant differences between the two drugs although the number of events was too small to draw any conclusion. One trial comparing lumiracoxib to rofecoxib reported a single bleed in the lumiracoxib arm.

Myocardial infarctions and cardiovascular thrombotic events
Two trials comparing lumiracoxib with celecoxib [CIC REMOVED-results of study 0109 and 0112].Three trials reported a total of five serious cardiovascular thrombotic events (see Figure 22). Overall there was no significant difference between the two drugs and the number of events was too small to allow sensible comparison. [CIC REMOVED-results of study 0109].

Hepatotoxicity
Data on hepatotoxicity was not included in our protocol for systematic review. However TARGET indicates that lumiracoxib is associated with significant hepatatoxicity: 2.7% of 9156 patients randomised to lumiracoxib had a hepatitis, defined as a rise in transaminases of three times above the upper limit of normal, compared with [CIC removed- percent in naproxen and ibuprofen group]. There were nine events of severe hepatitis, defined as a five fold increase in transaminases and a bilirubin of more than 51 μmol/l, with lumiracoxib and one case of hepatic failure.

Figure 18: Comparison of endoscopic ulcers with lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled estimate]

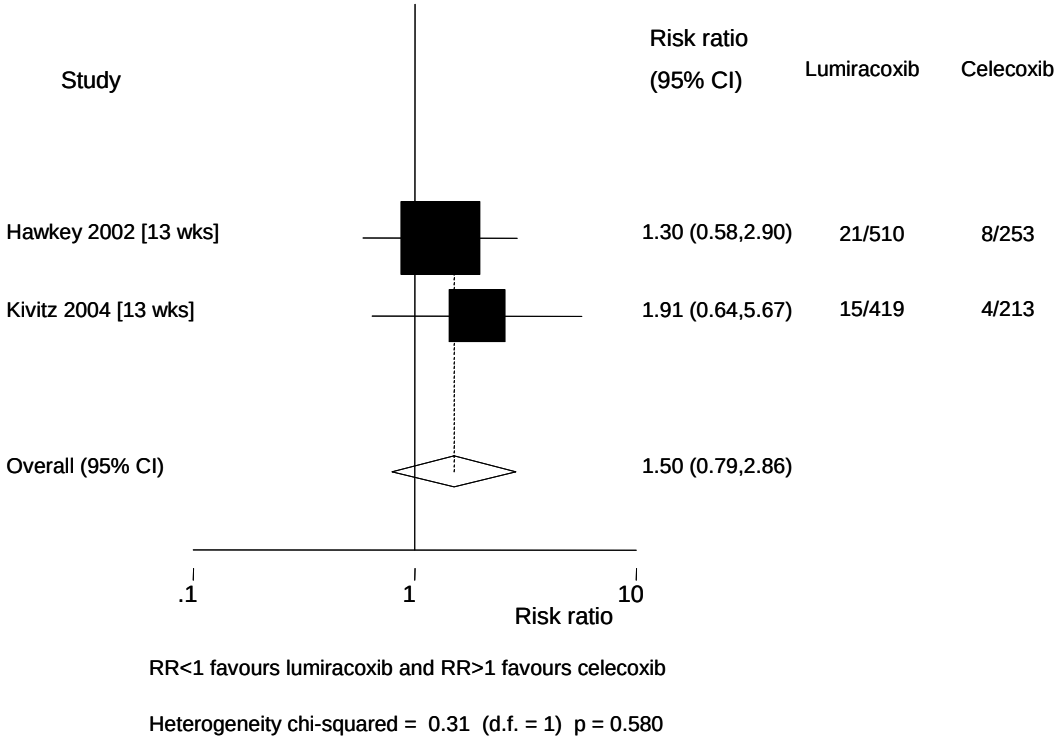

Figure 19: Comparison of POBs with lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled estimate

CIC figure removed- Overall Risk Ratio 1.46 95% CI: 0.23, 9.22]

Figure 20: Comparison of PUBs with lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled estimate]

[CiC figure removed- Overall Risk Ratio 0.97; 95% CI: 0.24, 3.87]

Figure 21: Comparison of MI with lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled estimate]

CiC figure removed- Overall Risk Ratio 1.46 95% CI: 0.15, 14.01

Figure 22: Comparison of serious CV thrombotic events with lumiracoxib (all doses) and celecoxib (all doses) [figure CIC except pooled estimate]

[CiC figure removed Overall Risk Ratio: 1.07; 95% CI: 0.24, 4.75]

1.2.10 Summary

- 15 RCTs were included. Studies compared lumiracoxib (100 to 1200 mg/day) to either placebo, non-selective NSAIDs (diclofenac, ibuprofen or naproxen) or COX-2 selective NSAIDs (celecoxib or rofecoxib).
- Lumiracoxib was of similar efficacy to non-selective NSAIDs for the symptomatic treatment of OA and RA, although the amount of trial evidence is small.
- Lumiracoxib is associated with significantly fewer GI-related adverse events and related withdrawals compared to non-selective NSAIDs except for hepatotoxicity which, in TARGET, was significantly increased for lumiracoxib compared with naproxen and ibuprofen.
- Lumiracoxib is associated with significantly fewer endoscopic ulcers than non-selective NSAIDs: this appears to be independent of patients' *H.Pylori* status.
- Lumiracoxib is associated with significantly fewer clinical and complicated GI events than non-selective NSAIDs in OA patients. This benefit of lumaricoxib appeared to be limited to patients not taking low dose aspirin but this conclusion is based on small numbers and requires confirmation.
- Lumiracoxib is associated with raised risk of clinical myocardial infarction events, particularly in OA patients not taking low dose aspirin and when compared to naproxen. This conclusion is based on limited data and requires confirmation.
- Lumiracoxib has not been compared with non-selective NSAIDs combined with a gastro-protective agent.
- The efficacy of lumiracoxib compared to celecoxib and rofecoxib appears to be dose-dependent. There is no significant difference between these COX-2 selective NSAIDs in terms of tolerability and safety based on short-term trials.

2 COST EFFECTIVENESS OF LUMIRACOXIB

No published economic evaluation of lumiracoxib was identified.

2.1 Methods

The analyses undertaken for the other COX-2 drugs (described in full in the main report) were repeated for lumiracoxib.

The Assessment Group Markov Model (AGM) was used and was again run for a time horizon of 5 years. The data inputs and assumptions that are not drug specific were not changed for lumiracoxib. The drug-specific inputs used in these analyses for lumiracoxib are reported in Tables 11 and 12 (see Tables 70 and 79, main assessment report) although hepatatoxicity, which is increased with lumiracoxib, has not been considered.

Table 11: Data for main Markov cycles

	Absolute or relative risk (RR)	**Source & Comment**
Risk of any GI event		
Ibuprofen	31.15 per 100 person yrs	CLASS[13]+.
Diclofenac	37.21 per 100 person yrs	CLASS[13]+
Lumiracoxib	RR 0.94 (95%CI 0.90 to 0.98)	Assessment group meta-analysis
No NSAID	RR 0.45	Assumed equivalent to lowest COX-2
Adding PPI	RR 0.40 (0.32 to 0.51)	Rostom et al[14] & Ekstrom et al[15]
Risk of clinical GI event (PUB)		
Ibuprofen	3.2 per 100 person yrs	CLASS[13]+
Diclofenac	1.19 per 100 person yrs	CLASS[13]+
Lumiracoxib	RR 0.47 (95% CI 0.36 to 0.60)	Assessment group meta-analysis.
No NSAID	RR 0.23	Assumed equivalent to lowest COX-2
Adding PPI	RR 0.4 (CI 0.32 to 0.51)	Rostom et al[14] & Ekstrom et al[15]
Risk of complicated GI event (POB)		
Ibuprofen	1.14 per 100 person yrs	CLASS[13]+
Diclofenac	0.48 per 100 person yrs	CLASS[13]+
Lumiracoxib	RR 0.34 (0.23 to 0.52)	Assessment group meta-analysis
No NSAID	RR 0.38	Assumed equivalent to lowest COX-2
Adding PPI	RR 0.4 (CI 0.32 to 0.51)	Rostom et al[14]& Ekstrom et al[15]
Risk of MI		
Ibuprofen	0.24/100 person years	CLASS[13]
Diclofenac	0.23/100 person years	CLASS[13]
Lumiracoxib	RR 1.71 (95% CI 0.86 to 3.37)	Assessment group meta-analysis
No NSAID	0.37/100 person years	See note below
Adding PPI	RR 1	Assumed PPI does not affect MI rates

+: non-aspirin users

Note: Effective antiplatelet therapy with aspirin reduces the risk of MI in low risk patients by about a third (risk reduction 30%; 95% CI 21% to 38%)[16]. Naproxen may provide a similar level of benefit and in a recent case controlled study ibuprofen had a protective effect similar to naproxen.[17] We have assumed that ibuprofen and diclofenac may have a similar beneficial effect on MI rate but we have explored the possibility that non-selective NSAIDs have no effect at all on MI rates.

Table 12: Data for initial cycle

Drug	Probability or RR	Source & Comment
Probability of taking no further NSAIDs in the first 3 months after prescription		
Ibuprofen	0.315	Langman et al.[18]
Diclofenac	0.265	Langman et al.[18]
Lumiracoxib	RR 1	Assumed same as ibuprofen
Probability of remaining on the same drug (alone)		
Ibuprofen	0.514	Langman et al.[18]
Diclofenac	0.603	Langman et al.[18]
Lumiracoxib	RR 1	Assumed same as ibuprofen
Probability of adding PPI to given NSAID		
Ibuprofen	0.026	Langman et al.[18]
Diclofenac	0.036	Langman et al.[18]
Lumiracoxib	RR 1	Assumed same as ibuprofen

In all cases, RR refers to comparison with ibuprofen.

The price of lumiracoxib was assumed to be £0.57 per day. This is based on information provided by the manufacturer.

The model was again run in two different forms: the 'full AGM', which includes an initial drug switching cycle, and the 'simpler AGM', where there is no initial cycle and no opportunity for the patient to switch NSAID.

2.2 Results for the simpler AGM

2.2.1 Results for the average patient

The model was initially run for a cohort of standard patients with starting age 58. Comparisons against ibuprofen (without PPI) are shown in Table 13 (see Table 72 main assessment report) and against diclofenac (without PPI) alone in Table 14 (see Table 73 main assessment report).

Table 13: Results comparing single COX-2 selective NSAIDs against ibuprofen

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
Ibuprofen	£520.01		3.19151		
Lumiracoxib	£1,226.72	£706.71	3.19737.	0.00586	£121,000

Eff = effectiveness in QALY. Incr = Incremental. ICER = Incremental Cost-Effectiveness Ratio (£/QALY).

Table 14: Results comparing single COX-2 selective NSAIDs against diclofenac

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
Diclofenac	£530.69		3.1875		
Lumiracoxib	£1,226.72	£696.03	3.19737	0.00987	£70,500

For both ibuprofen and diclofenac as comparators, lumiracoxib is associated with a higher cost (i.e. positive incremental cost) and a small increase in effectiveness (i.e. positive incremental effectiveness), measured in terms of QALYs. The magnitude of the incremental costs is virtually identical for the two comparator drugs but the incremental effects, and therefore the ICERs, are quite different.

In order to explore the sensitivity of our results to variation in the comparator we also compared COX-2 selective NSAIDs against non-selective NSAIDs with PPI. The results are shown in Tables 15 and 16 (see Tables 74 & 75 main assessment report).

Table 15: Results comparing single COX-2 selective NSAIDs against ibuprofen plus PPI

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
Ibuprofen+PPI	£950.35		3.22033		
Lumiracoxib	£1,226.72	£276.37	3.19737	-0.02296	D

Table 16: Results comparing single COX-2 selective NSAIDs against diclofenac plus PPI

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
Diclofenac+PPI	£970.55		3.21803		
Lumiracoxib	£1,226.72	£256.17	3.19737	-0.02066	D

In both cases, non-selective NSAID plus PPI dominates the COX-2 selective NSAID (i.e. the COX-2 is associated with both a higher cost and poorer effectiveness). This is because in this model the relative risk of GI events for adding PPI to a non-selective NSAID is lower (more favourable) than the relative risk for COX-2 selective NSAIDs.

2.2.2 Results for high risk patients

We also ran this model for patients with previous history of GI events. In this case, it would be standard practice to compare COX-2 selective NSAID alone against non-selective NSAID plus PPI. The results are shown in Tables 18 and 19 (see Tables 76 & 77 main assessment report).

Table 17: Results comparing single COX-2 selective NSAIDs against ibuprofen plus PPI for patients with previous history of GI events

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
Ibuprofen+PPI	£980.50		3.21381		
Lumiracoxib	£1,231.72	£251.22	3.19203	-0.02178	D

D means COX-2 inhibitor strategy is dominated by NSAID strategy

Table 18: Results comparing single COX-2 selective NSAIDs against diclofenac plus PPI for patients with previous history of GI events

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
Diclofenac+PPI	£982.23		3.21538		
Lumiracoxib	£1,231.72	£249.49	3.19203	-0.02335	D

The results show a very similar pattern to those reported in Tables 15 and 16.

2.3 Results for the full AGM

2.3.1 Results for the average patient

The full model was initially run for a cohort of standard patients with starting age 58. The results are as in Table 19 (see Table 80 main assessment report).

Table 19: Base case results

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.24		3.20428		
COX-2 Second	£493.00	£51.76	3.2039	-0.00038	(Dominated)
COX-2 First	£825.30	£384.05	3.20661	0.00233	£165,000

Incremental costs and effectiveness relative to "No COX-2" in each case

These results indicate that the use of lumiracoxib second line (after initially trying ibuprofen) is dominated by the 'No COX-2' strategy (i.e. ibuprofen followed by diclofenac, if required) – it is associated with both a higher cost and a poorer level of effectiveness. Lumiracoxib first line is associated with a higher cost and higher effectiveness than the 'No COX-2' strategy. Strategies involving the use of lumiracoxib (either first or second line) look very unattractive from a cost-effectiveness point of view.

2.3.2 Sensitivity Analysis

We have conducted a number of univariate sensitivity analyses where the sensitivity of the results of the full AGM are explored. The parameters varied are the relative risks of GI events and the risk of MI.

Varying relative risks of GI events

For this analysis, we set the relative risks of GI events to the lower and upper 95% confidence limits shown in Table 11. We set the risks of any GI event, clinical GI event, and complicated GI event simultaneously to low values and then to high values. To maintain our assumption that risks for "No NSAID" were equivalent to the lowest COX-2, we have changed the risks for "No NSAID" in line with the other changes. Thus, the costs and effects for the comparator strategy of "No COX-2" alter, even though this is a sensitivity analysis about relative risks of COX-2 selective NSAIDs compared to ibuprofen. The results from using the lower values are shown in Table 20, while the results from the higher values for the same drug are in Table 21. In general terms, and in line with the analyses reported in the main report for the other COX-2 drugs, the results are sensitive to variation in the value of the relative risk of GI events.

Table 20: Results with relative risk for all types of GI event at the lower confidence limits (favouring COX-2 selective NSAIDs)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£408.12		3.20925		
COX-2 Second	£457.48	£49.36	3.21046	0.00121	£40,900
COX-2 First	£788.60	£331.12	3.21434.	0.00389.	£85,200

Table 21: Results with relative risk for all types of GI event at the upper confidence limits (favouring non-selective NSAIDs)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£476.43		3.19748		
COX-2 Second	£531.25	£54.82	3.19462	-0.00286	(Dominated)
COX-2 First	£864.97	£388.55	3.19594	-0.00154	(Dominated)

Varying risk of MI

We also varied the relative risk of MI (compared to ibuprofen) across its 95% confidence limits shown in Table 11. Results are reported for the lower limits in Table 22 and for the upper limits in Table 23. In general terms, the results are not highly sensitive to variation in the value of the risk of MI events.

Table 22: Results with relative risk for MI at the lower confidence limits (favouring COX-2 selective NSAIDs)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.24		3.20428		
COX-2 Second	£491.57	£50.33	3.20411	-0.00017	(Dominated)
COX-2 First	£815.42	£374.18	3.20804.	0.00377	£99,300

ICER for "COX-2 First" relative to "No COX-2"

Table 23: Results with relative risk for MI at the upper confidence limits (favouring non-selective NSAIDs)

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£441.24		3.20428		
COX-2 Second	£495.80	£54.55	3.20349	-0.00079	(Dominated)
COX-2 First	£844.56	£403.31	3.20382.	-0.00046	(Dominated)

As a separate analysis, we tested the view that NSAIDs do not protect against MI: this was done by setting the "No NSAID" risk for MI to be 0.23/100 person years, the same as the better non-selective NSAID (diclofenac). These results are reported in Table 24 (see Table 98 main assessment report). This made very little difference to the base case results.

Table 24: Results with MI risk for No NSAID 0.23/100 person years – same as better non-selective NSAID (diclofenac).

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
No COX-2	£436.42		3.20498		
COX-2 Second	£488.00	£51.58	3.20462	-0.00036	(Dominated)
COX-2 First	£820.35	£383.93	3.20732	0.00235	£164,000

Incremental costs and effectiveness relative to "No COX-2" in each case

2.3.3 Results for high risk patients

The most important high risk group consists of patients with previous GI history. For these patients, the comparison is between lumiracoxib (taken originally without PPI) and non-selective NSAIDs taken with PPI. The results are shown in Table 24 (see Table 85 main assessment report).

Table 25: Results for patients with previous GI history

Strategy	Cost	Incr Cost	Eff	Incr Eff	ICER
COX-2 Second	£720.61		3.21123		
No COX-2	£752.74	£32.13	3.21636	0.00512	£6,270
COX-2 First	£865.72	£112.98	3.20583	-0.01052	(Dominated)

Once again, these results are broadly consistent with those analyses using the simpler AGM. The results indicate that use of lumiracoxib second line (after initially trying ibuprofen) is associated with a lower cost but also reduced effectiveness when compared to the 'No COX-2' strategy (i.e. ibuprofen followed by diclofenac, if required). This gives an ICER of £6,720 for the move from the strategy of lumiracoxib second line to the strategy of no COX-2. It is clearly not cost-effective to use lumiracoxib either first or second line according to these results.

2.4 Summary

- Using the simpler AGM, with ibuprofen or diclofenac alone as the comparator, lumiracoxib is associated with higher costs (i.e. positive incremental costs) and small increases in effectiveness (i.e. positive incremental effectiveness), measured in terms of QALYs. The ICERs exceed £70,000 per QALY.

- When the simpler AGM was run using ibuprofen or diclofenac combined with PPI as the comparator, the results indicate dominance for the NSAID plus PPI strategies. Lumiracoxib looks very unattractive from a cost-effectiveness point of view. This applies both to standard patients and to "high-risk" patients defined in terms of previous GI events.

- The full model produced results broadly in line with the simpler model.

3 DIFFERENCES IN ASSESSMENT GROUP MODEL AND COMPANY MODEL RESULTS

This section discusses the differences in the results of the economic analyses (i.e. the cost per quality of life adjusted (QALY) results) for the assessment group model (AGM) and those of the company models. The results of the company analyses are summarised the main assessment report (Section 5.3 to 5.6). For the purposes of comparability, the AGM results referred to here come from the model without the initial cycle (i.e. the 'simpler AGM').

The comparison does not include etodolac or lumiracoxib as no company model was submitted for either. The discussion considers separately the results for 'average' and 'high' risk patients.

'Average' risk patients

- For comparability, this section discusses the AGM results for COX-2 selective NSAIDs compared to non-selective NSAIDs (not combined with a PPI) in average risk patients (see Table 26).
- The ICERs for meloxicam and etoricoxib are incremental cost per QALYs, and the company model and assessment group model results for 'average' OA and RA patients are similar (see Table 26).
- For valdecoxib, comparability of the AGM and company results is complicated by the fact that the AGM ICER is in the form of cost per QALY while the company ICER is a cost per life year gained (LYG). Nevertheless, given that the additional years of life with COX-2's will be at a utility of less than 1, the company and AGM ICER results are also similar. Given their similarity and that they are all around or below £30,000 per QALY, the results for etoricoxib, valdecoxib and meloxicam will not be discussed further in this section.
- There are notable differences in the company and AGM ICERs for celecoxib and rofecoxib – the AGM ICERs being considerably less attractive than those of the company. These differences are not explained by the company use of LYG and the AGM use of QALYs as the outcome measure. The reasons for theses differences are explored below.
- *Celecoxib ICERs:* an important contribution to the difference in celecoxib ICERs is that the company (Pfizer) model (ACCESS) does not explicitly take into account a difference in MI risk between COX-2 and non-selective NSAIDs, while the Birmingham AGM model does take into account this difference[1] (see Table 27). The AGM sensitivity analysis indicates that the ICERs for all COX-2's are sensitive to variations in the relative MI risk (see main assessment report, section 5.6.2). Furthermore, it can be seen from Table 28 that the relative estimates for GI AEs, POBs and PUBs used in the company model greatly favour celecoxib. The company submission states the source of the GI events as the SUCCESS trial while the AGM estimates are

[1] Not so much an issue for valdecoxib ICER, which is also based on this model, as B/ham meta-analysis shows RR for MI <1.00

based on a meta-analysis of all potentially includable trials, including SUCCESS. Although the costs of celecoxib used by the company model and AGM appear similar, the non-selective NSAIDs costs used by the company are considerably higher (see Table 29). This difference in non-selective NSAID cost would again favour the company model ICER for celecoxib.

- *Rofecoxib ICERs:* the company (MSD) and AGM models used for rofecoxib appear relatively similar in structure. Both include GI AEs, major GI and MI events, as with the AGM model, it is stated in the company submission that these estimates are sourced from a meta-analysis of trials. The GI parameter values used by the company appear to fall within the 95% CIs of the AGM values. However, the relative risk of MI for rofecoxib in the company base case model set to a value of 1.00 in contrast to a relative risk of MI in the AGM of 2.92 (95% CI: 1.29 to 6.60). Although the costs of rofecoxib used by company model and AGM appear similar, the non-selective NSAIDs costs used by the company are considerably higher (see Table 4). This difference in non-selective NSAID cost would again favour the company model QALY ICER for rofecoxib.
- In conclusion, not surprisingly, the cost effectiveness results for COX-2's are dependent on model structure, effectiveness and cost parameter values. The company model and AGM both show that etoricoxib, valdecoxib and meloxicam for 'average' patients have a cost per QALY ICER at or below £30,000 relative to a non-selective agent. However, based on a more appropriate model structure (which includes MI events) and utilisation of parameters values based on available trial evidence, the Birmingham AGM model ICERs for celecoxib and rofecoxib are substantially less attractive than those of the company (i.e. >>£30,000 per QALY).

'High risk' patients

The Boehringer Ingelheim and Pfizer reports present results for 'high-risk patients' comparing COX-2 selective NSAID to non-selective NSAID alone. The Merck Sharp Dohme report gives an ICER for COX-2 selective NSAID compared to a non-selective NSAID combined with a PPI in average risk patients. However, unlike the report of the AGM-based analyses, none of the company submissions gives explicit results for the comparison of COX-2 selective NSAID compared to a non-selective combined with a PPI in high-risk patients. No direct comparison of the cost effectiveness results for the AGM and company models for high risk patients is, therefore, possible.

Table 26: Comparison of company models & assessment group model (AGM) [with no initial switching cycle] results for 'average' risk patients

	NSAID cost per patient	COX-2 cost per patient	NSAID QALY	COX-2 QALY	Incremental cost per patient	Incremental QALY	ICER	Comments
Rofecoxib								
MSD	£125	£296	CIC	CIC	+£171	+0.0154	£11,104	1-year time horizon
AGM	£519	£1560	3.1875	3.1980	+£1029	+0.01055	£97,500	
Etoricoxib								
MSD	£132	3518	0.6426	0.6510	+£178	+0.0084	£22,143	1-year time horizon
AGM	£519	£1516	3.1875	3.2206	+£985	+0.0331	£29,800	
Meloxicam								
BI	£811	£929	3.1850	3.1988	+£118	+0.0139	£8,543	
AGM	£519	£855	3.1875	3.2064	+£324	+0.01985	£17,100	
Celecoxib								
Pfizer	£59	£140	0.0074**	0.00164**	+£81	+0.00576**	£16,063**	**LYG & 1-year time horizon
AGM	£519	£932	3.1875	3.1945	+£932	+0.00704	£132,000	
Valdecoxib								
Pfizer	£59	£134	0.0074**	0.00347**	+£75	+0.00393**	£19,083**	**LYG & 1-year time horizon
AGM	£519	£1466	3.1875	3.21817	+£936	+0.03067	£30,500	

Notes:

All ICER estimates reported for each model are those most in favour of COX-2

Company ICER estimates are slightly different to those reported in company submissions & represent rounding errors

Source of results cited in this table all come from the main assessment report i.e. AGM results see Table 73; MSD rofecoxib results see Table 61; MSD etoricoxib results see Table 64; Pfizer celecoxib and valdecoxib results see Table 57; BI meloxicam results not reported by company and represent run of the BI model by assessment team.

Table 27: Comparison of 'structure' of company models and assessment group model (AGM)

Model name	**ACCESS**	**MSD**	**Maetzel**	**AGM**
COX-2's	Celecoxib, valdecoxib	Rofecoxib, etoricoxib	Meloxicam	All COX-2's
Company	Pfizer	As above	BI	Assessment group
Efficacy	Assumed equivalent between COX-2 & NSAIDS	Assumed equivalent between COX-2 & NSAIDS	Assumed equivalent between COX-2 & NSAIDS	Assumed equivalent between COX-2 & NSAIDS
GI parameters used	GI AEs POBs PUBs GI w/drawals	PUBs Lower GI events*	Any GI event PUBs POBs	Any GI event PUBs POBs
MI included?	No	Yes	Yes	Yes
Time horizon	1-year	1-year	5-year	5-years
Source of parameter values	Celecoxib – SUCCESS Valdecoxib – Meta-analysis	Meta-analysis	SELECT or MELISSA	Meta-analysis

Notes:
***: set to RR 1.00 in base case analysis**

Table 28: Comparison of clinical effectiveness parameter values used by company models and assessment group model (AGM)

	Celecoxib		Valdecoxib		Rofecoxib		Etoricoxib		Meloxicam	
Parameters	**Pfizer***	**AGM**	**Pfizer***	**AGM**	**MSD***	**AGM**	**MSD***	**AGM**	**BI**	**AGM**
GI AE	0.76 (GI discomfort)	0.95 (0.76 to 1.21)	0.65 (GI discomfort)	0.64 (0.523 to 0.78)	CIC/0.90	0.84 (0.45 to 1.60)	0.80	0.45 (0.22 to 0.92)	Not included separately	Not included separately
POB	0.17 (serious GI event)	0.57 (0.34 to 0.97)	0.38 (serious GI event)	0.38 (0.17 to 0.86)	Not included	0.40 (0.23 to 0.70)	Not included	0.46 (0.07 to 3.10)	0.208	0.52 (0.36 to 1.05)
PUB	0.23 (ulcer)	0.64 (0.46 to 0.89)	0.12 (ulcer)	0.12 (0.03 to 0.59)	CIC/0.37	0.43 (0.32 to 0.57)	0.53	0.23 (0.05 to 1.08)	0.139/0.371	0.57 (0.30 to 1.08)
MI	Not included	1.87 (1.06 to 3.30)	Not included	0.23 (0.06 to 0.90)	1.00	2.92 (1.29 to 6.60)	1.00	0.46 (0.07 to 3.10)	0.139/0.149	1.87 (0.6 to 3.30)

Notes:
***the parameter descriptions for the company model are the nearest match to those of the AGM.**

Table 29: Daily drug costs included in company models and assessment group model (AGM)

	BI	MSD	Pfizer	AGM
Non-selective NSAID		0.28*	0.23 (generic) 0.44 (branded)	
Ibuprofen				0.11
Diclofenac	0.3343			0.13
Piroxicam	0.1193			
COX-2				
Celecoxib			0.75 (OA) 0.90 (RA)	0.718 (OA) 1.436 (RA)
Etodolac			0.52	0.52
Etoricoxib		0.82	0.82 (OA) 0.85 (RA)	0.82
Meloxicam	0.3333 (OA) 0.4633 (RA)		0.38	0.33 (OA) 0.46 (RA)
Rofecoxib		0.80	0.85 (OA) 0.89 (RA)	0.77
Valdecoxib			0.77	0.77
PPI		0.71*		
Omeprazole				0.46
Pantoprazole	0.8446			
NSAID + PPI			0.93	
Analgesics				0.05
Acetaminophen (paracetamol)	0.3760			

Notes:
***:The average daily cost within a drug class (NSAID, PPI, H_2-antagonist) was obtained using data from the MediPlus database and taking the sum of individual products weighted by market share.**

Appendix 1: Details of characteristics of included randomised controlled trials

Trial label (protocol number), Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)+	Concurrent low dose (≤325mg/d) aspirin (%)++	Other comments (underline the appropriate response; provide further details if "yes")
Schnitzer 2000, Novartis Study 0104, multinational, 4 weeks [1]	Lumiracoxib 100mg per day (50mg bd)	98	61.3	68	7.4	NR	NR	NR[3]	OA (of hip or knee) GPA allowed in during the trial (no) Included patients on steroids (No) and/or anticoagulants (can't tell) Included patients with positive H. pylori (HP) status and/or on HP therapy (can't tell) Included functional class (can't tell)
	Lumiracoxib 200mg per day (100mg bd)	96	59.8	70	6.6				
	Lumiracoxib 400mg per day (200mg bd)	99	59.5	75	6.9				
	Lumiracoxib 400mg per day (400mg od)	99	60.1	59	6.3				
	Diclofenac 75mg per day bd	94	59.7	68	6.3				
	Placebo	97	61.5	67	8.0				
Hawkey 2002 Novartis Study 0126, **[CiC removed],**, 13 weeks treatment [2]	Lumiracoxib 200mg per day (200mg od)	264	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	NR	OA [CiC] [CiC removed]
	Lumiracoxib 400mg per day (400mg od)	260	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]		
	Celecoxib 200mg per day (200mg od)	258	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]		
	Ibuprofen 2400mg per day (800mg tds)	260	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]		

Trial label (protocol number), Country Duration[a]	**Intervention & comparator[b]**	**N[c]**	**Age (years)[d]**	**% female**	**Disease duration (years)[d]**	**Prior NSAIDs (%)**	**Prior GI events (%)+**	**Concurrent low dose (≤325mg/d) aspirin (%)++**	**Other comments (underline the appropriate response; provide further details if "yes")**
Benevolenskaya 2003, Novartis Study 2316, [CiC], 4 weeks[3] ([CiC-location]	Lumiracoxib 100mg od Placebo	122 122	[CiC] [CiC]	[CiC] [CiC]	[CiC] [CiC]	[CiC] [CiC] (	[CiC] [CiC]	[CiC] [CiC]	OA (knee or hip) [CiC removed]
Fleischmann 2003 Novartis Study 0109, [CiC] 13 weeks, [CiC removed – location]	Lumiracoxib 200mg per day (200mg od) Lumiracoxib 400mg per day (400mg od) Celecoxib 200mg per day (200mg od) Placebo	465 465 446 232	[CiC] [CiC] [CiC] [CiC]	[CiC] [CiC] [CiC] [CiC]	[CiC] [CiC] [CiC] [CiC]	[CiC] [CiC] [CiC] [CiC]	[CiC] [CiC] [CiC] [CiC]	[CiC]	OA (knee) [CiC removed]

Trial label (protocol number), Country Duration[a]	**Intervention & comparator[b]**	**N[c]**	**Age (years)[d]**	**% female**	**Disease duration (years)[d]**	**Prior NSAIDs (%)**	**Prior GI events (%)+**	**Concurrent low dose (≤325mg/d) aspirin (%)++**	**Other comments (underline the appropriate response; provide further details if "yes")**
Gifka 2003, Novartis Study 2319, [CiC] 4 weeks[5]	Lumiracoxib 200mg per day (200mg od) Lumiracoxib 400mg per day (400mg od) Placebo	205 193 196	[CiC] [CiC] [CiC]	[CiC] [CiC] [CiC]	[CiC] [CiC] [CiC]	[CiC] [CiC] [CiC]	[CiC]	[CiC]	OA (hand) [CiC]
Tannenbaum 2004 Novartis Study 0112, International multicentre 13 weeks [6]	Lumiracoxib 200 mg per day (200 mg od) Lumiracoxib 400 mg per day (400 mg od) Celecoxib 200 mg per day (200 mg od) Placebo	487 491 481 243	[CiC] [CiC] [CiC] [CiC]	[CiC] [CiC] [CiC] [CiC]	[CiC] [CiC] [CiC] [CiC]	[CiC] [CiC] [CiC] [CiC]	[CiC] [CiC] [CiC] [CiC]	[CiC] [CiC] [CiC] [CiC]	OA of the knee [CiC]

Trial label (protocol number), Country Duration[a]	**Intervention & comparator[b]**	**N[c]**	**Age (years)[d]**	**% female**	**Disease duration (years)[d]**	**Prior NSAIDs (%)**	**Prior GI events (%)+**	**Concurrent low dose (≤325mg/d) aspirin (%)++**	**Other comments (underline the appropriate response; provide further details if "yes")**
Novartis Study 0128, [CiC removed]	[CiC]	[CiC] [CiC] [CiC]	[CiC] [CiC] [CiC]	[CiC] [CiC] [CiC]	[CiC] [CiC] [CiC]	[CiC] [CiC] [CiC] ([CiC])	[CiC] [CiC] [CiC]	[CiC] [CiC] [CiC]	[CiC removed]

Trial label (protocol number), Country Duration[a]	**Intervention & comparator[b]**	**N[c]**	**Age (years)[d]**	**% female**	**Disease duration (years)[d]**	**Prior NSAIDs (%)**	**Prior GI events (%)+**	**Concurrent low dose (≤325mg/d) aspirin (%)++**	**Other comments (underline the appropriate response; provide further details if "yes")**
Novartis Study 2307, [CiC removed]	[CiC]	[CiC] [CiC]	[CiC] [CiC]	[CiC] [CiC]	[CiC] [CiC]	[CiC] [CiC]	[CiC] [CiC]	[CiC] [CiC]	[CiC removed]

Trial label (protocol number), Country Duration[a]	Intervention & comparator[b]	N[c]	Age (years)[d]	% female	Disease duration (years)[d]	Prior NSAIDs (%)	Prior GI events (%)+	Concurrent low dose (≤325mg/d) aspirin (%)++	Other comments (underline the appropriate response; provide further details if "yes")
TARGET trial Novaritis Studies 0117 (vs naproxen) and Study 2332 (vs ibuprofen), International 52 weeks [7] [8,9]	Lumiracoxib 400mg per day (400mg od)	9156	63.5	76.4	[CiC]	[CiC]	[CiC]	24%	OA of hip, knee, hand, cervical or lumbar spine and symptoms for >3 months. [CiC]
	Naproxen 1000mg per day (500mg bd)	4754	63.6	76.6	[CiC]	[CiC]	[CiC]	25.%	CIC
	ibuprofen 2400mg per day (800mg tds)	4415	63.3	76.1	[CiC]	[CiC]	[CiC]	22%	CIC Included patients on anticoagulant (no).
						[CiC]			[CiC]
								(Patients were stratified for aspirin use)	Stratification according to age: age <65 yr, 65-74 years, >74 years. Patients also stratified according to aspirin use.
Guesens 2003, Novartis Study 0111, multinational, 26 weeks [10] CIC removed-location	Lumiracoxib 200mg per day (200mg od)	280	CIC	CIC	CIC	NR	CIC	NR	RA CIC REMOVED
	Lumiracoxib 400mg per day (400mg od)	281	CIC	CIC	CIC		CIC		
	Naproxen 1000mg per day (500mg bd)	279	CIC	CIC	CIC		CIC		
	Placebo	284	CIC	CIC	CIC		CIC		

Trial label (protocol number), Country Duration[a]	**Intervention & comparator[b]**	**N[c]**	**Age (years)[d]**	**% female**	**Disease duration (years)[d]**	**Prior NSAIDs (%)**	**Prior GI events (%)+**	**Concurrent low dose (≤325mg/d) aspirin (%)++**	**Other comments (underline the appropriate response; provide further details if "yes")**
Kivitz 2004 Novartis 0110, multinational, 13 weeks [11]	Lumiracoxib 400mg per day (400mg od) Lumiracoxib 800mg per day (800mg od) Celecoxib 400mg per day (200mg bd) Ibuprofen 2400mg per day (800mg tds)	227 227 223 216	52.4 50.6 51.7 52.2	78.0 80.6 77.6 79.6	CIC CIC CIC CIC	CIC CIC CIC CIC	NR	NR	RA GPA allowed in during the trial (no) Included patients on steroids (yes) and/or anticoagulants (no). Proportions of patients on these drugs: low dose corticosteroids CIC respectively for lumiracoxib 400mg, 800mg, celecoxib 200mg and placebo groups. Included patients with positive H. pylori (HP) status and/or on HP therapy (yes) Included functional class (I, II or III)
Scott 2003, Novartis Study 2312, [CiC removed]	Lumiracoxib 800mg per day (800mg od) Lumiracoxib 1200mg per day (1200mg od) Naproxen 1000mg per day (500mg bd)	[CiC] [CiC] [CiC]	[CiC] [CiC] [CiC]	[CiC] [CiC] [CiC]	NR	NR	[CiC]	[CiC] [CiC] [CiC]	RA [CIC removed] Included functional class (I, II or III)
Novartis Study 0105, [CiC removed]	L[CiC removed]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC removed])

Trial label (protocol number), Country Duration[a]	**Intervention & comparator[b]**	**N[c]**	**Age (years)[d]**	**% female**	**Disease duration (years)[d]**	**Prior NSAIDs (%)**	**Prior GI events (%)+**	**Concurrent low dose (≤325mg/d) aspirin (%)++**	**Other comments (underline the appropriate response; provide further details if "yes")**
Novartis Study 0114, [CiC removed]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC removed]
Novartis A2335, [[CiC removed]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC removed]

[a]Duration of follow-up [b]Dose per day [c]Number of randomised [d]Values are means unless otherwise specified
S=steroid/A=aspirin/Ac=anticoagulant/GPA=gastroprotective agents +Gastrointestinal ulcer ++if allowed; state if not allowed

Appendix 2: Details of quality assessment of included randomised controlled trials

Trial label (protocol number)	Appropriate method of randomisation	Adequate concealment	Double blind	Intention to treat analysis	Loss to follow up reported	Total Jadad score /5
Schnitzer 2000, Novartis Study 0104	CT	CT	Y	Y	Y	4
Hawkey 2002, Novartis Study 0126	[CiC]	[CiC]	Y	[CiC]	[CiC]	[CiC]
Benevolenskaya 2003, Novartis study 2316	[CiC]	[CiC]	Y	[CiC]	[CiC]	[CiC]
Fleischmann 2003, Novartis Study 0109	[CiC]	[CiC]	Y	[CiC]	[CiC]	[CiC]
Grifka 2003, Novartis Study 2319	[CiC]	[CiC]	Y	[CiC]	[CiC]	[CiC]
Tannenbaum 2004, Novartis Study 0112	[CiC]	[CiC]	Y	[CiC]	[CiC]	[CiC]
Novartis Study 0128	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]
Novartis Study 2307	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]
TARGET, Novartis Study 0117/A2332	Y	Y	Y	Y	Y	5
Geusens 2003, Novartis Study 0111	[CiC]	[CiC]	Y	[CiC]	[CiC]	[CiC]
Kivitz 2004, Novartis Study 0110	CT	CT	Y	Y	Y	4
Scott 2003, Novartis Study 2312	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]
Novartis Study 0105	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]
Novartis Study 0114	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]
Novartis Study A2335	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]	[CiC]

Appendix 3: Summary of efficacy results of lumiracoxib versus celecoxib and rofecoxib and comparison of efficacy stratified by doses

Summary of efficacy results of lumiracoxib versus celecoxib and rofecoxib

	Celecoxib (200-400mg per day)				Rofecoxib (25mg per day)			
Lumiracoxib	**VAS Pain difference Mean (95% CI)**	**VAS Global efficacy difference Mean (95% CI)**	**ACR 20 RR (95% CI)**	**Withdrawals due to lack of efficacy RR (95% CI)**	**VAS Pain difference Mean (95% CI)**	**VAS Global efficacy difference Mean (95% CI)**	**ACR 20 RR (95% CI)**	**Withdrawals due to lack of efficacy RR (95% CI)**
100mg/day	No trials	No trials	No trials	No trials	No trials	No trials	No trials	No trials
200mg/day	1.08 (-3.08 to 5.25)* [3]	1.31 (-2.85 to 5.48)* [3]	CiC Removed [1]	1.17 (0.90 to 1.51) [4]	No trials	No trials	No trials	No trials
>200mg/day	*-0.67 (-3.90 to 2.56)* [3]*	-0.55 (-2.66 to 1.56) [3]	CiC Removed [1]	1.05 (0.81 to 1.36) [5]	CiC Removed [1]	CiC Removed [1]	No trials	0.87 (0.37 to 2.04) [2]
OA only	-1.63 (-3.69 to 0.43) [2]	-1.16 (-3.26 to 0.93) [2]	No trials	0.83 (0.59 to 1.16) [3]	CiC Removed [1]	CiC Removed [1]	No trials	0.87 (0.37 to 2.04) [2]
RA only	[CiC removed] [1]	[CiC removed] [1]	[CiC removed] [1]	*1.44 (1.06 to 1.95) [2]*	No trials	No trials	No trials	No trials
All trials	0.26 (-3.45 to 3.98)* [3]	0.53 (-2.83 to 3.89)* [3]	[CiC removed] [1]	1.12 (0.89 to 1.40) [5]	CiC Removed [1]	CiC Removed [1]	No trials	0.87 (0.37 to 2.04) [2]

* heterogeneity P<0.10 & random effects model used; [ ]: N trials; † one trial reported zero events in both arms. For mean differences, negative values favours lumiracoxib and positive values favours comparators.

Comparison of efficacy outcomes between lumiracoxib and celecoxib stratified by celecoxib doses

	Celecoxib							
Lumiracoxib	**VAS Pain difference Mean (95% CI)**		**VAS Global efficacy difference Mean (95% CI)**		**ACR 20 RR (95% CI)**		**Withdrawals due to lack of efficacy RR (95% CI)**	
	200mg/day	**400mg/day**	**200mg/day**	**400mg/day**	**200mg/day**	**400mg/day**	**200mg/day**	**400mg/day**
100mg/day	No trials	No trials	No trials	No trials	No trials	No trials	No trials	No trials
200mg/day	-1.02 (-3.43 to 1.39) [2]	CiC Removed [1]	-0.8 (-3.25 to 1.65) [2]	CiC Removed [1]	No trials	CiC Removed [1]	0.89 (0.61 to 1.31) [3]	CiC Removed [1]
>200mg/day	-2.24 (-4.58 to 0.10) [2]	CiC Removed [1]	-1.53 (-3.92 to 0.87) [2]	CiC Removed [1]	No trials	CiC Removed [1]	0.76 (0.51 to 1.14) [3]	1.35 (0.96 to 1.91) [2]
OA only	-1.63 (-3.69 to 0.43) [2]	No trials	-1.16 (-3.26 to 0.93) [2]	No trials	No trials	No trials	0.83 (0.59 to 1.16) [3]	No trials
RA only	No trials	CiC Removed [1]	No trials	[CiC removed) [1]	No trials	[CiC removed] [1]	No trials	[CiC removed] [2]
All trials	-1.63 (-3.69 to 0.43) [2]	CiC Removed) [1]	-1.16 (-3.26 to 0.93) [2]	CiC Removed [1]	No trials	CiC Removed [1]	0.83 (0.59 to 1.16) [3]	1.44 (1.06 to 1.95) [2]

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