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Lumiracoxib

Katherine A. Lyseng-Williamson and *Monique P. Curran*

Adis International Limited, Auckland, New Zealand

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Abstract

▲ Lumiracoxib is a highly selective and potent cyclo-oxygenase (COX)-2 inhibitor, with a novel structure that conveys weakly acidic properties and a unique pharmacological profile. It is rapidly absorbed, with a relatively short plasma half-life.

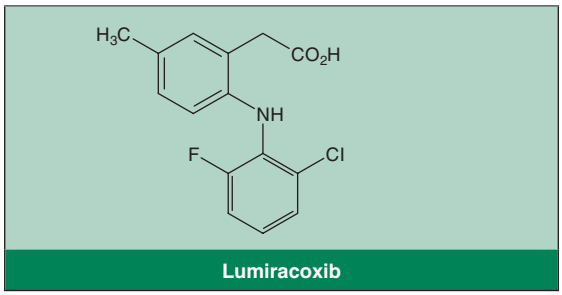
▲ In well designed clinical trials of 1–52 weeks' duration in patients with osteoarthritis (OA) or rheumatoid arthritis, the efficacy of oral lumiracoxib 100–400 mg/day in decreasing pain intensity and improving functional status was greater than that with placebo and similar to those with nonselective NSAIDs or celecoxib 200mg once daily.

▲ In single- and multiple-dose well designed trials in patients with acute pain associated with primary dysmenorrhoea, dental or orthopaedic surgery or tension-type headache, lumiracoxib 100–800mg once daily was more effective in relieving acute pain than placebo or controlled-release oxycodone 20mg, and was at least as effective as selective COX-2 inhibitors or nonselective NSAIDs.

▲ Lumiracoxib was generally well tolerated in clinical trials, with a similar overall tolerability profile to those of placebo and other COX-2-selective inhibitors.

▲ In a large 52-week safety trial in patients with OA, lumiracoxib 400mg once daily had a rate of gastrointestinal ulcer complications that was approximately one-third to one-quarter of that of ibuprofen 800mg three times daily or naproxen 500mg twice daily. Lumiracoxib was not associated with an increase in cardiovascular events.

Features and properties of lumiracoxib (Prexige®)	
Indications	
Osteoarthritis (OA), rheumatoid arthritis, moderate-to-severe acute pain and primary dysmenorrhoea	
Mechanism of action	
Cyclo-oxygenase-2-selective inhibitor	
Dosage and Administration	
Approved dosage (in the UK)	100–200 mg/day (OA)
	400 mg/day (acute pain)
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (single-dose 200mg in healthy volunteers)	
Mean peak plasma concentration (C_{max})	4180 ng/mL
Median time to C_{max}	2–3h
Mean area under the plasma concentration-time curve from 0 to infinity	16 700 ng • h/mL
Mean oral bioavailability	74%
Metabolism	Hepatic
Elimination half-life	3–6h
Adverse events	
Generally well tolerated, with fewer gastrointestinal ulcer-related complications than nonselective NSAIDs	



Lumiracoxib

Conventional NSAIDs (which are nonselective cyclo-oxygenase [COX] inhibitors) are effective in treating inflammation and pain, but are associated with an increased risk of adverse events, primarily involving the gastrointestinal (GI) tract.[1] The analgesic and anti-inflammatory effects of nonselective NSAIDs appear to result mainly from the inhibition of COX-2 and their GI adverse events are primarily due to the inhibition of COX-1.[1] COX-2-selective inhibitors are designed to minimise the adverse effects associated with nonselective NSAIDs, while optimising the efficacy of COX-2 inhibition in the treatment of inflammation and pain.[2]

Lumiracoxib (Prexige®)[1] is a novel oral COX-2-selective inhibitor. Unlike other COX-2-selective inhibitors (which are non-acidic sulfonamides or methylsulfones), lumiracoxib is a compound with weakly acidic properties derived from phenylacetic acid, which may account for its distinct pharmacokinetic profile.[1,2] Some data for lumiracoxib are currently available only as abstracts, posters or media releases.[3-23]

1. Pharmacodynamic Profile

- *In vitro*, lumiracoxib inhibited COX-2 activity more potently than COX-1 activity (concentrations required to inhibit 50% of enzyme activity [IC_{50}] 0.1 vs 70 μmol/L).[3] Compared with celecoxib and rofecoxib, lumiracoxib had similar potency in inhibiting COX-2 activity (measured using prostaglandin [PG] E_2 production), but less potency in inhibiting COX-1 activity (measured using thromboxane [TX] B_2 production).[3] The COX-2 selectivity IC_{80} ratio (TXB_2 production : PGE_2 production) of lumiracoxib was 500, which was higher than that of the COX-2-selective inhibitors rofecoxib and celecoxib (150 and 30, respectively).[3]
- In *ex vivo* whole blood assays that measured COX-2 and COX-1 in a similar manner, inhibition of COX-2 was dose dependent[3,4] and selective for COX-2 over COX-1 following single-[3,4] or multiple-dose[24] oral lumiracoxib 25–800mg.[3,4,24] Lumiracoxib 200mg twice daily[25] or 800mg once daily[24] inhibited COX-1 to a significantly ($p < 0.001$) lesser extent[24,25] than naproxen 500mg twice daily in whole blood[24] or serum.[25] COX-2 was inhibited to a similar extent by both agents.[24]
- Compared with placebo, lumiracoxib (at dosages up to 300mg twice daily for 9 days), did not affect platelet aggregation in 40 healthy male volunteers.[5]

2. Pharmacokinetic Profile

The pharmacokinetic profile of oral lumiracoxib has been studied in healthy volunteers,[4-7,25-30] and in patients with osteoarthritis (OA),[8] rheumatoid arthritis (RA)[9,31] or moderate hepatic impairment[32] (n = 4–65). Unless otherwise noted, values pertain to pharmacokinetic parameters of oral lumiracoxib in healthy volunteers.

- Lumiracoxib is rapidly absorbed throughout the GI tract,[28] with a mean bioavailability of 74%.[6] In healthy volunteers[4,6,25] and patients with OA,[8] the peak plasma concentration (C_{max}) of lumiracoxib was reached after a median time of approximately 2–3 hours. Lumiracoxib demonstrates time-independent pharmacokinetics and steady state is rapidly achieved.[8]
- The relationship between dose (25–800 mg/day) and the C_{max} and area under the plasma concentration-time curve (AUC) values of lumiracoxib after both single[4,5,8] and repeated[5,8] administration is linear. In a dose escalation study (n = 48),[4] the AUC_∞ values of single-dose lumiracoxib 100, 200 and 400mg were 8350, 16 700 and 40 900 ng • h/mL; the corresponding C_{max} values were 2420, 4180 and 6740 ng/mL.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

• Lumiracoxib had both a low volume of distribution at steady state (9L)[6] and a low mean plasma clearance (≈8 L/h).[6,26] The drug undergoes only modest first-pass metabolism; most (81–91%) of the plasma radioactivity of single-dose [^{14}C]lumiracoxib 400mg at timepoints up to 2.5 hours post-dose were accounted for by the unchanged drug.[26]

• Prior to excretion, lumiracoxib is extensively metabolised primarily by oxidation by cytochrome P450 (CYP) 2C9.[26] The only major metabolite demonstrated to be active is the 4′-hydroxy-5-carboxy derivative.[26] After administration of a single-dose of radiolabelled lumiracoxib 400mg, 54.1% (3.3% as the unchanged drug) and 42.7% (1.9% as the unchanged drug) of the initial radioactivity were recovered in the urine and faeces. Almost the entire dose (96.8%) was recovered within 168 hours.[26] The elimination half-life ($t_{1/2}$) of single-dose lumiracoxib 100–400 mg/day is approximately 3–6 hours.[4,5]

• At day 7 in 22 patients with RA, the mean concentration of lumiracoxib 400 mg/day in knee joint synovial fluid was initially lower than that in plasma, but became higher at 5 hours post-dose and remained higher for the remainder of the 28-hour assessment.[31] Mean $AUC_{12–24}$ values were 2.6-fold higher in synovial fluid than in plasma.

• The pharmacokinetic profile of lumiracoxib does not appear to be influenced by sex, age, bodyweight[8] or moderate hepatic impairment (Child-Pugh score 7–9).[32]

• Despite its metabolism primarily by CYP2C9, the pharmacokinetics of lumiracoxib were not affected to a clinically significant extent by coadministration of CYP2C9 inhibitors (e.g. fluconazole)[27] or substrates (e.g. warfarin).[7] The pharmacokinetics of single-dose lumiracoxib were also not affected by coadministration with multiple-dose omeprazole or single-dose aluminium hydroxide/magnesium hydroxide antacid.[29]

• Coadministration of lumiracoxib 400mg once daily did not affect the pharmacokinetic profile of the triphasic oral contraceptive ethinylestradiol/levonorgestrel in a 28-day study in 35 healthy women[30] or of methotrexate in a 7-day study in 18 patients with RA.[9]

3. Therapeutic Efficacy

The therapeutic efficacy of oral lumiracoxib has been investigated in randomised, double-blind, comparator-controlled trials in patients with OA,[10-13,18,19,33-35] RA[14] and acute pain.[15-17,36-38]

With the exception of a few trials that were described as single centre[17,36,37] or did not state the number of centres,[10] trials were conducted in multiple centres. Lumiracoxib was administered once daily in all trials, excepting one 4-week dose-ranging trial in patients with OA.[33] Where stated, patients could receive rescue medication with paracetamol (acetaminophen),[11-14,34-38] hydrocodone/paracetamol,[16,36,37] pethidine (meperidine)[16] or morphine.[15,16]

In Patients with Arthritis

Osteoarthritis

The efficacy of lumiracoxib 100–400 mg/day has been compared with that of placebo, nonselective NSAIDs and celecoxib in the symptomatic relief of OA in 1-,[10] 4-[11,12,33] and 13-week[13,34] trials, a 39-week extension study[18,19] of one[34] of the 13-week trials, and the 52-week safety study (TARGET [the Therapeutic Arthritis Research and GI Event Trial]; see section 4 for further design details).[35]

Among the inclusion criteria was a pain intensity measurement of ≥40[11-13,33,34] or ≥50mm[10] on a 100mm visual analogue scale (VAS), or 3 points (moderate pain) on a 5-point categorical scale.[35] In many trials, patients underwent a washout period (2–7 days)[10-13,33,34] for previous NSAIDs.

The primary measure of efficacy was generally the change in OA pain intensity in the target joint from baseline (assessed using a 100mm VAS[10-13,33,34] or 5-point categorical scale[35]). Other efficacy measures included patient's and physician's global assessments of disease activity (GADA),[10-13,33-35] assessments of functional status (using the Western Ontario and McMaster Universi-

ties OA Index [WOMAC™] total, pain, difficulty in performing daily activities [DPDA] or stiffness scores,[10,11,13,33,34] or Australian/Canadian OA Hand Index total and subscale scores[12]) and effects on articular cartilage.[19]

- Lumiracoxib is associated with a rapid onset of action.[10] In a 7-day trial in 364 patients with OA of the knee, the pain intensity difference (PID) between baseline and after the first dose (mean of the 3- and 5-hour assessments) was significantly greater with lumiracoxib 400mg than with placebo (19.8 vs 13.4mm; p = 0.004).[10] Lumiracoxib was significantly superior to placebo for overall pain relief throughout the study. In contrast, there was no significant difference between celecoxib 200mg and placebo in providing pain relief after the first dose.
- In 4-week trials (n = 244–594), lumiracoxib (50, 100 or 200mg twice daily[33] or 100,[11] 200[12] or 400mg[12,33] once daily) was significantly ($p \leq 0.05$) more effective in reducing pain intensity from baseline than placebo in patients with OA of the knee or hip[11,33] or hand[12] (estimated treatment difference in favour of lumiracoxib 8.41–15.5mm).[11,12,33] In addition, lumiracoxib generally improved patient's and physician's GADA and functional status scores to a significantly ($p < 0.05$) greater extent than placebo.[11,12,33]
- In the 4-week dose-ranging trial,[33] lumiracoxib 100–400 mg/day had similar efficacy to diclofenac 75mg twice daily with regard to pain relief and improvement in functional status in patients with OA of the knee or hip at study end. Despite the relatively short $t_{1/2}$ of lumiracoxib (section 2), lumiracoxib 400mg once daily was as effective as lumiracoxib 200mg twice daily.[33]
- In two similar 13-week trials in patients with OA of the knee (n = 1702[34] and 1600[13]), lumiracoxib 200 and 400mg once daily reduced pain and improved functional status to a significantly greater extent than placebo ($p < 0.01$) and to a similar extent as celecoxib 200mg once daily after 13 weeks' treatment (see figure 1 for results from Tannenbaum et al.[34]). No significant differences were observed between the two dosages of lumiracoxib.[13,34] Improvements were achieved by the first measurement (week 2) and were maintained until the end of both trials.[13,34]
- The efficacy of lumiracoxib was maintained in the 39-week extension[18,19] of one[34] of the 13-week trials. Long-term pain relief and improved functional status with lumiracoxib 200 (n = 411) or 400 mg/day (n = 419) was similar to that with celecoxib 200 mg/day (n = 405).[18] In a radiological subgroup analysis of 781 patients, neither lumiracoxib nor celecoxib had any significant effect on minimum joint-space width.[19]
- Although TARGET was a safety study, it also assessed efficacy.[35] The clinical efficacy of lumiracoxib 400mg once daily (n = 9117) was similar to that of ibuprofen 800mg three times daily or naproxen 500mg twice daily (n = 9127). Although statistically significant improvements in patient's and doctor's GADAs (both $p < 0.03$) were shown with lumiracoxib relative to the NSAIDs (pooled data from the ibuprofen and naproxen substudies), the differences were not clinically significant. Change in joint pain intensity and the amount of paracetamol used as rescue medication were not significantly different between the treatment groups.[35]

Rheumatoid Arthritis

- In 1124 patients with symptomatic RA in a 26-week trial, the proportion of patients achieving an American College of Rheumatology 20 response at 13 weeks (primary endpoint) was significantly greater with lumiracoxib 200 or 400mg once daily than with placebo (41.1% and 42.7% vs 32.4%; $p < 0.05$); the response rate with naproxen 500mg twice daily (39.1%) was not significantly different from that with placebo or lumiracoxib.[14] No significant differences between active treatment groups were seen at any timepoint (2, 4, 13, 20 and 26 weeks) during the study.

In Patients with Acute Pain

Clinical trials in patients with moderate-to-severe pain relating to dental[36,37] or orthopaedic[15,16] surgery, primary dysmenorrhoea[38] or tension-type headache[17] have investi-

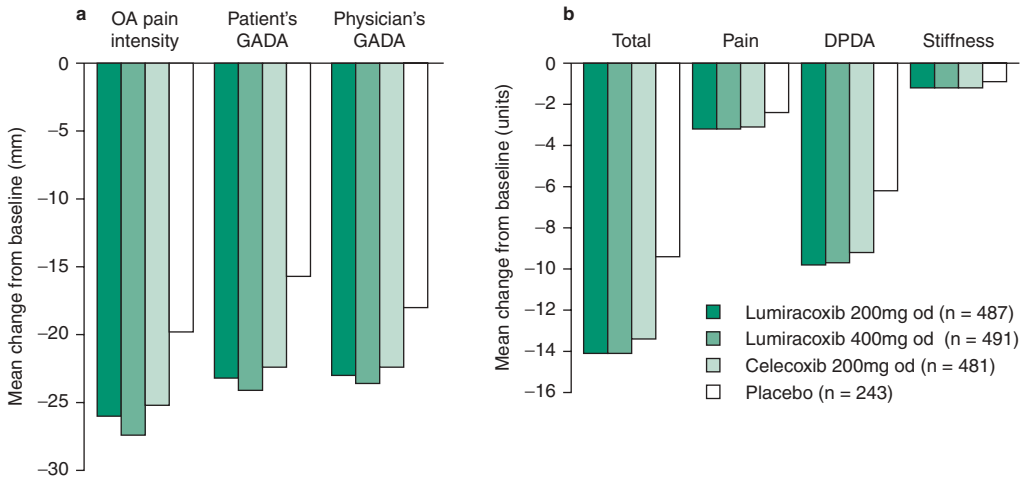


Fig. 1. Comparative efficacy of oral lumiracoxib and celecoxib in patients with osteoarthritis (OA) of the knee. Changes from baseline in (**a**) OA pain intensity in the target joint, patient's global assessment of disease activity (GADA) and physician's GADA (assessed using 100mm visual analogue scales) and (**b**) Western Ontario and McMaster Universities OA Index questionnaire scores at 13 weeks in a randomised, double-blind, placebo-controlled, multicentre trial.[34] A decrease in score is consistent with an improvement in symptoms. All active treatments were significantly ($p < 0.01$) superior to placebo with respect to each parameter. **DPDA** = difficulty in performing daily activities; **od** = once daily.

gated the efficacy of single-[15-17,36,37] or multiple-dose[15,16,38] lumiracoxib 100–800mg once daily compared with placebo, other COX-2-selective inhibitors or nonselective NSAIDs. Primary efficacy endpoints included 4-point categorical or 100mm VAS PID from baseline to various timepoints,[15,16,36] summed (time-weighted) PID over 8 hours (SPID-8)[15,16,37,38] and time to onset of analgesia.[17]

Postsurgical Dental Pain

- Single-dose lumiracoxib 100[36] or 400mg[36,37] provided more rapid and effective analgesia than placebo, and was as effective as or superior to single doses of ibuprofen 400mg[36] or other COX-2-selective inhibitors (rofecoxib 50mg[37] and celecoxib 200mg[37]) for up to 24 hours in patients with postoperative dental pain.[36,37] Patients had moderate-to-severe pain after extraction of at least two impacted third molars.
- As measured by mean categorical PID scores over 12 hours, lumiracoxib 400mg (n = 50) and ibuprofen 400mg (n = 51) were significantly more effective than placebo (n = 50) at all timepoints from 1 hour onwards, and lumiracoxib 100mg was significantly more effective than placebo from 1.5 to 9 hours (all $p < 0.05$).[36]
- Assessing pain relief over 8 hours (categorical SPID-8 scores), lumiracoxib 400mg demonstrated superior pain relief to rofecoxib 50 mg ($p < 0.05$), celecoxib ($p < 0.001$) and placebo ($p < 0.001$) in a pooled analysis of two trials (n = 355 in a primary study and 155 in a supplementary study).[37]
- The median time to onset of analgesia was significantly faster with lumiracoxib 100 or 400mg (37–52 minutes) than with placebo[36,37] or celecoxib[37] (>12 hours for both; $p < 0.001$) and was similar to that with ibuprofen[36] or rofecoxib[37] (42[36] and 51[37] minutes). The median time to use of rescue medication was significantly longer with lumiracoxib 400mg than with placebo,[36,37] celecoxib[37] or ibuprofen[36] (all $p \leq 0.01$).

Postorthopaedic Surgical Pain

- In single- and multiple-dose trials in patients with moderate-to-severe post-orthopaedic surgical pain at 48 hours after hip or knee arthroplasty, pain relief provided by lumiracoxib 400[15,16] or 800mg[16] was greater than that with placebo and similar to that with naproxen 500mg in one trial

(n = 180),[15] and was generally greater than that with placebo and controlled-release (CR) oxycodone 20mg in another trial (n = 240).[16]

- In the single-dose phase of the trials, lumiracoxib was significantly more effective than placebo[15,16] or CR oxycodone (all $p < 0.02$)[16] as measured by the least square means of categorical SPID-8 scores. There were no differences in efficacy between CR oxycodone and placebo[16] or lumiracoxib 400mg and naproxen.[15] The median time to first use of rescue medication was significantly (all $p < 0.05$) longer with lumiracoxib 400mg or naproxen than with placebo (3.8 and 3.9 vs 2.0 hours),[15] and with lumiracoxib 400 and 800mg than with CR oxycodone or placebo (7.3 and 9.2 vs 4.2 and 3.1 hours).[16]
- In the multiple-dose phase (up to 96 hours post first dose) of the trials, lumiracoxib 400 mg/day was significantly ($p = 0.05$) more effective (as measured by mean categorical and/or VAS PID scores) than placebo[15,16] or CR oxycodone 20mg twice daily (which showed efficacy similar to placebo)[16] at most 12-hour timepoints, and was equally effective as naproxen 500mg twice daily.[15]

Primary Dysmenorrhoea

- The efficacy (as assessed by least square mean categorical SPID-8 scores) of lumiracoxib 400mg once daily for up to 3 days was significantly greater than that of placebo ($p < 0.001$) and similar to that of a COX-2-selective inhibitor (rofecoxib 50mg once daily) or an NSAID comparator (naproxen 500mg twice daily) in two three-way crossover trials in women aged ≥18 years with moderate-to-severe primary dysmenorrhoea (n = 84 and 99; reported together in one paper).[38]
- Lumiracoxib, rofecoxib and naproxen were also significantly ($p < 0.05$) superior to placebo with regards to other efficacy variables (e.g. categorical PID scores at most timepoints, total [time-weighted] pain relief from 0 to 8 hours, and patient global evaluation of treatment effect).[38]

Tension-Type Headache

- In 150 patients with moderately severe-to-severe pain associated with an episodic tension-type headache, single-dose lumiracoxib 200 or 400mg (within 1 hour of headache onset) provided significantly more rapid pain relief than placebo (median time to onset of analgesia 47 and 41 minutes vs >3 hours; $p < 0.001$).[17] Both doses of lumiracoxib were also more effective than placebo (as measured by PID and pain relief scores at 1, 2 and 3 hours, and the summed measure of combined scores over 3 hours; $p < 0.05$).

4. Safety and Tolerability

The tolerability profile of lumiracoxib has been assessed in clinical trials (section 3), GI tolerability studies,[20,39] and TARGET.[35,40] TARGET,[41] a large, randomised, double-blind 52-week safety trial, compared the GI[35] and cardiovascular[40] safety profiles of lumiracoxib 400mg once daily (two or four times the recommended dosage for OA) with those of the maximum therapeutic dosage of two nonselective NSAIDs in patients with OA. The trial was divided into two substudies: lumiracoxib versus ibuprofen 800mg three times daily (n = 4376 and 4397) and lumiracoxib versus naproxen 500mg twice daily (n = 4741 and 4730).[41] As prespecified, data from the two substudies have been pooled for analysis; the two comparator agents (ibuprofen and naproxen) are hereafter referred to as the NSAIDs when discussing pooled substudy data.[41] Patients had primary OA in the hip, knee, hand, cervical spine or lumbar spine, with at least moderate baseline pain in the target joint, and were aged ≥50 years.

In order to evaluate the effect of low-dose aspirin (acetylsalicylic acid) on GI and cardiovascular outcomes, 24% of patients were receiving aspirin 75–100 mg/day at enrolment, including patients with a history of ischaemic cardiovascular disease or with a high relative cardiovascular risk (must have received aspirin for primary or secondary cardiovascular prophylaxis for ≥3 months) and those already taking low-dose aspirin regardless of their cardiovascular risk profile.[41] Patients at a high risk for cardiovascular disease who were not receiving low-dose aspirin were excluded. Among other exclusion criteria were the chronic use of gastroprotective medications (e.g. proton pump inhibitors, misopros-

tol and histamine H_2 receptor antagonists), use of anticoagulant or antiplatelet therapy other than aspirin, evidence or recent history of a cardiovascular or GI event or condition, and evidence of a hepatic, renal or blood coagulation disorder.[41]

Baseline characteristics of the treatment groups were similar within each substudy;[35,40,41] of note, the lumiracoxib and NSAID groups had similar baseline incidences of major independent risk factors for cardiovascular disease, such as hypertension (46% vs 44%), dyslipidaemias (20% for both) and diabetes mellitus (8% vs 7%).[40] There were, however, some differences between the substudies (e.g. the proportion of patients with high cardiovascular risk or cardiovascular history [14% vs 10%][35] or previous vascular risk [12% vs 8%][40] was higher in the naproxen than ibuprofen substudy).

- Lumiracoxib was generally well tolerated in clinical trials (section 3), GI tolerability studies,[20,39] and TARGET.[35] In short-term (up to 96 hours) clinical trials in patients with acute pain[15-17,36-38] and also in longer-term (up to 26 weeks) clinical trials in patients with arthritis,[10-14,20,33,34,39] the tolerability profile of single- or multiple-dose lumiracoxib 100–400 mg/day was comparable to those of other analgesics. In all treatment groups, the majority of adverse events were of mild-to-moderate severity.

- In TARGET,[35] the proportions of patients with adverse events, serious adverse events and adverse events requiring discontinuation were similar in the lumiracoxib and NSAID groups (79% vs 80%, 6% for both, and 16% vs 18%, respectively).[35] The most common adverse events were GI events, including dyspepsia and upper abdominal pain. Fewer lumiracoxib than NSAID recipients reported upper abdominal pain (10% vs 12.6%; significance not reported). The combined incidence of GI and cardiovascular events was significantly lower with lumiracoxib than with the NSAIDs (0.98% vs 1.46%; $p = 0.0014$) or ibuprofen (0.69% vs 1.27%; $p = 0.0025$). Although the combined incidence was numerically lower with lumiracoxib than with naproxen (1.24% vs 1.63%), the between-group difference was not significant.[35]

- Transitory elevations in liver function parameters that returned to normal following withdrawal from treatment have been shown with lumiracoxib.[35] In TARGET,[35] the proportion of patients with transaminase levels greater than three times the upper limit of normal was significantly greater with lumiracoxib than with the NSAIDs (2.6% vs 0.6%; $p < 0.0001$).
- The incidence of serious hepatic events leading to jaundice was not significantly different between lumiracoxib, ibuprofen and naproxen; jaundice was reported in six (0.07%) lumiracoxib recipients compared with two (0.05%) ibuprofen recipients and one (0.02%) naproxen recipient in TARGET.[23] The lumiracoxib and NSAID groups had similar incidences of major renal adverse events (defined as a ≥100% increase in serum creatinine from baseline or proteinuria ≥3 g/L) [0.5% vs 0.4%].[35]

Gastrointestinal Events

- Lumiracoxib is associated with a significantly lower risk of GI-related events (e.g. gastroduodenal ulcers, erosions and bleeding) than nonselective NSAIDs.[20,21,35,39] GI events with lumiracoxib are not dose related.[20]
- TARGET, the largest GI outcomes study in OA performed to date, found that the rate of definite or probable ulcer complications (clinically significant bleeding, perforation or obstruction from erosive or ulcer disease) with lumiracoxib was approximately one-third to one-quarter of that with the NSAIDs in the overall population (figure 2) and in the population not receiving aspirin (0.20% vs 0.92%) [both $p < 0.0001$].[35] In the population receiving aspirin, the rate of ulcer complications was numerically lower with lumiracoxib than with the NSAIDs (0.69% vs 0.88%); however, the between-group difference was not significant. Definite or probable ulcer complications most frequently presented as haematochezia or melaena.[35]
- Similar results are shown in each substudies of TARGET.[35] The proportion of patients with ulcer complications was significantly (all $p \leq 0.0006$) lower with lumiracoxib than with ibuprofen or naproxen in the overall population (figure 2) and in

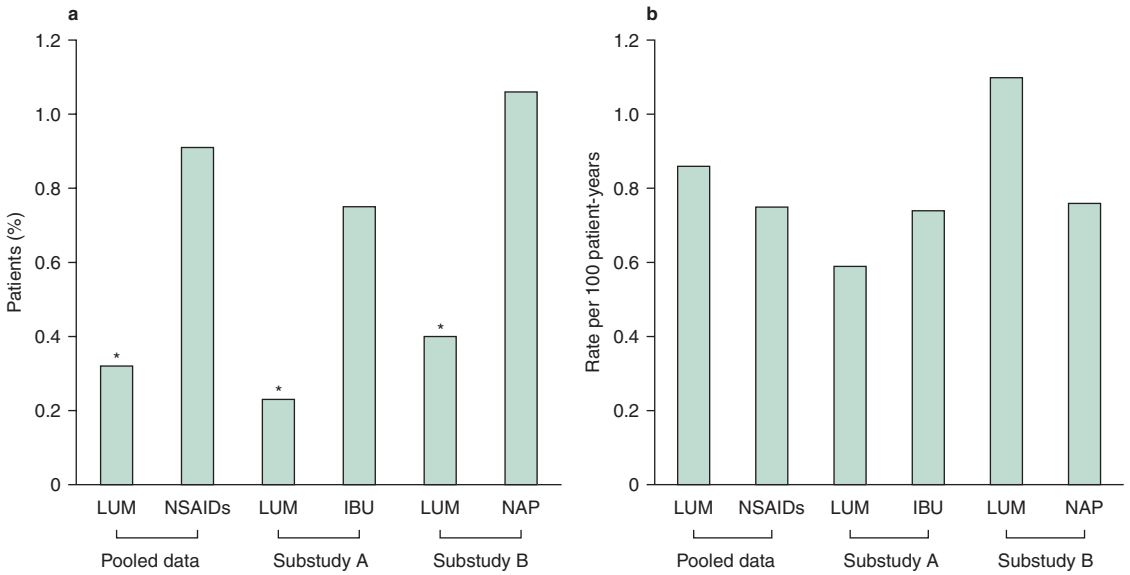


Fig. 2. Comparative gastrointestinal (GI) and cardiovascular safety of oral lumiracoxib 400mg once daily (LUM), ibuprofen 800mg three times daily (IBU) and naproxen 500mg twice daily (NAP) in patients with osteoarthritis. (**a**) Incidence of definite or probable upper GI complications (clinically significant bleeding, perforation or obstruction from erosive or ulcer disease)[35] and (**b**) rate per 100 patient-years of confirmed or probable composite primary cardiovascular endpoint events (myocardial infarction, stroke and cardiovascular death)[40] in a randomised, double-blind 52-week study. Data from substudy A (LUM vs IBU; n = 4376 and 4397) and substudy B (LUM vs NAP; n = 4741 and 4730) were pooled (LUM vs NSAIDs; n = 9117 and 9127). * $p \leq 0.0006$.

the population not receiving aspirin (0.15% vs 0.82% and 0.25% vs 1.02%), but not in the population receiving aspirin (0.51% vs 0.52% and 0.84% and 1.17%).

- Moreover, in the overall population, lumiracoxib reduced the risk of anaemia (acute or chronic) by 52%, 60% and 40% compared with, respectively, the NSAIDs, ibuprofen or naproxen (all $p \leq 0.0137$).[35] The rate of symptomatic uncomplicated ulcers (ulcers discovered when endoscopy was performed for dyspepsia) was also lower with lumiracoxib than with NSAIDs (0.64% vs 1.13%; $p = 0.0003$).

- In randomised, multicentre endoscopic 13-week studies in patients with OA (n = 1011)[20] or RA (n = 893),[39] lumiracoxib 200–800mg once daily was associated with cumulative rates of gastroduodenal ulcers of ≥3mm diameter that were significantly ($p < 0.01$) lower than those with ibuprofen 800mg three times daily[20,39] and similar to those with celecoxib 200mg once[20] or twice[39] daily.

- In the pooled analysis of 15 trials,[21] the combined incidence of perforations, obstructions, symptomatic ulcers and bleedings with lumiracoxib (200 or 400 mg/day) and other COX-2-selective inhibitors (celecoxib 200 or 400 mg/day and rofecoxib 25 mg/day) was approximately one-tenth that with nonselective NSAIDs (twice-daily diclofenac 75mg or twice-daily naproxen 500mg) [1.65 and 1.43 vs 13.68 events per 100 patient-years exposure].

Cardiovascular Events

- In the overall population in TARGET,[40] the incidence of the primary cardiovascular events endpoint (composite of confirmed or probable myocardial infarction [MI; clinical or silent], ischaemic or haemorrhagic stroke and cardiovascular death) was low (0.65 % with lumiracoxib vs 0.55% with the NSAIDs). There were no significant differences between lumiracoxib and the NSAIDs, ibuprofen or naproxen in the rate of primary cardiovascular endpoint events per 100 patient-years (figure 2).[40]

• In TARGET, the number of primary cardiovascular endpoints was, as expected, greatest in the population receiving low-dose aspirin (the population at high cardiovascular risk); no significant differences between treatment groups were shown.[40] The rate of primary cardiovascular endpoint events per 100 patient-years was 1.51 with lumiracoxib and 1.46 with the NSAIDs in the population receiving low-dose aspirin compared with 0.86 and 0.75 in the overall population and 0.66 and 0.53 in the population not receiving aspirin.

• Moreover, the rates of all confirmed or probable MIs, stroke, cardiovascular death, vascular events of ischaemic origin, deep vein thrombosis and pulmonary embolism were not significantly different between lumiracoxib and the pooled or individual NSAIDs.[40] Although not statistically significant, lumiracoxib was associated with more MIs than naproxen in the population not taking aspirin (ten vs four events), which may indicate a possible antithrombotic effect with naproxen.

• Lumiracoxib affected systolic and diastolic blood pressures to a significantly lesser extent than the pooled or individual NSAIDs (all $p \leq 0.0002$) in TARGET.[40] The least squares mean change from baseline in systolic blood pressure was 0.4mm Hg with lumiracoxib compared with 2.1mm Hg for the NSAIDs; the corresponding values for diastolic blood pressure were −0.1 and 0.5mm Hg (both $p < 0.0001$).

• In pooled data from 15 clinical trials of lumiracoxib in 10 438 patients with OA or RA, the rates of blood pressure increase, oedema and increased body weight in patients with or without hypertension at baseline with lumiracoxib 200 or 400 mg/day compared favourably with those with nonselective NSAIDs.[22]

5. Dosage and Administration

Formal prescribing information is not currently available for lumiracoxib; however, the recommended doses for OA and acute pain would be those approved in the UK (i.e. oral lumiracoxib 100–200 mg/day for OA and 400 mg/day for moderate-to-severe acute pain associated with primary dysmenorrhoea, dental surgery or orthopaedic surgery[42]).

6. Lumiracoxib: Current Status

Lumiracoxib is approved for the symptomatic relief of OA and the short-term relief of moderate-to-severe acute pain resulting from primary dysmenorrhoea, dental surgery or orthopaedic surgery in the UK,[42] and OA, RA, acute pain and primary dysmenorrhoea in several Latin American countries.[43,44] It has shown clinical efficacy in well designed trials in these indications and was generally well tolerated, with better GI tolerability than nonselective NSAIDs. In the safety trial TARGET, lumiracoxib demonstrated a significant GI benefit, without affecting cardiovascular safety.

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Correspondence: *Katherine A. Lyseng-Williamson*, Adis International Ltd, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz