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Lumiracoxib in the management of osteoarthritis and acute pain

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Lumiracoxib is a highly selective COX-2 inhibitor with a novel chemical structure and a relatively short plasma half-life. It has been approved in > 40 countries for the symptomatic treatment of osteoarthritis and/or acute pain related to primary dysmenorrhoea and dental or orthopaedic surgery. In these conditions, lumiracoxib has proved to be as effective as standard doses of conventional NSAIDs and other COX-2 selective inhibitors (coxibs). According to the Therapeutic Arthritis Research Gastrointestinal Trial, which enrolled 18,325 patients with osteoarthritis, lumiracoxib 400 mg/day (four times its recommended dosage) was associated with a significant decrease in the risk of ulcer complications compared with naproxen 1000 mg/day and ibuprofen 2400 mg/day, at least in the population not taking low-dose aspirin. The atherothrombotic potential of NSAIDs, especially coxibs, has been much debated. In this respect, available data do not suggest that lumiracoxib may be associated with an increased hazard of cardiovascular events compared with non-selective NSAIDs. Finally, lumiracoxib may be an effective and safe drug provided both physicians and patients will comply with its approved indications and contraindications.

Keywords: acute pain, COX-2 inhibitors, lumiracoxib, NSAIDs, osteoarthritis

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1. Introduction

Osteoarthritis (OA) is by far the most common disease to affect synovial joints, particularly the knee, hip and hand. It is characterised pathologically by progressive loss of articular cartilage resulting in narrowing of joint space on plain radiographs, along with varying degrees of new bone formation at the joint margins (osteophytes), subchondral bone changes and mild synovitis [1]. Clinical features of OA include pain that typically worsens with weight-bearing or activity, short-lasting stiffness after inactivity and limitation of joint motion associated with disability and impaired quality of life. Although it is a chronic disorder of multifactorial aetiology, OA is strongly age-related in such a way that most people older than 70 years of age have radiological evidence of OA in some joints [1]. However, symptoms are present in a smaller proportion depending on the joint involved. Radiographic signs of knee OA are present in 30% of subjects aged over 55 – 65 years, around one third of whom are symptomatic [2]. The prevalence of hip OA is lower, ranging from 3 – 11% in Western populations aged over 35 years, but it is often symptomatic [3]. Thus, OA is an important societal burden both in terms of morbidity and cost. Furthermore, this burden is expected to increase with the increasing prevalence of obesity and increasing longevity of the population. As there is no known cure for the disease, medical management of patients with OA aims at alleviating pain and improving function and quality of life [2-4]. For this purpose, existing guidelines recommend the combination of non-pharmacological with pharmacological treatment modalities [2-4]. In this respect, paracetamol is considered to be the most appropriate first-line analgesic, mainly because of its overall safety profile [2-5]. Unfortunately, paracetamol is less effective than NSAIDs, including COX-2 selective inhibitors (coxibs) [5]. Moreover, a

majority of patients with OA prefer NSAIDs to paracetamol [5]. Accordingly, existing guidelines advise the prescription of an NSAID in patients who are unresponsive to paracetamol and/or patients with moderate-to-severe pain, and in those in whom signs of joint inflammation are present [2-4].

Acute pain is a problem in many clinical settings. Most patients undergoing surgery experience pain, the severity and duration of which depend on the procedure used. For example, the greatest levels of pain and discomfort following third molar extraction are experienced during the first day following surgery [6]. Therefore, it is essential that an analgesic agent has a rapid onset of action [6]. Effective pain management is not only important from an ethical perspective, but has also been shown to improve postoperative recovery and outcome [7]. There is compelling evidence that NSAIDs as a class are superior to paracetamol and weak opioids in dental surgery, whereas no conclusion can be made regarding the relative efficacy of NSAIDs and paracetamol in orthopaedic surgery [8]. Interestingly, NSAIDs are commonly used as an adjunct to opioid-based analgesia in major surgery in order to provide effective and sustained pain relief [8]. Dysmenorrhoea is also a very common acute painful condition [9]. In adolescents and young adult females, it is usually primary (functional). Owing to its high prevalence, dysmenorrhoea is the leading cause of recurrent short-term school or work absenteism [9]. Although lower abdominal cramping is the most frequent symptom, many patients suffer from other menstruation-associated symptoms, such as diarrhoea, nausea, fatigue, light-headedness, headache and dizziness [9]. Symptoms usually last less than 1 day, but pain may persist up to days 2 or 3 of the menstrual period [9]. Numerous clinical trials have documented the efficacy of both conventional NSAIDs and coxibs. These findings are consistent with the central role of prostaglandins (PGs) in the pathophysiology of dysmenorrhoea [9]. Finally, women suffering from primary dysmenorrhoea should be offered NSAIDs as a first-line treatment for the relief of pain and improved daily activity, unless they have a contraindication to the use of NSAIDs [9]. Effective treatment is initiated with the onset of bleeding and/or associated symptoms, and should not be necessary for more than 2 – 3 days [9].

2. Overview of the market

As a result of their analgesic and anti-inflammatory properties, NSAIDs are widely used effective medicines in the treatment of arthritis and many other painful conditions. In fact, > 110 million prescriptions for NSAIDs are filled in the US annually, and ~ 24 million prescriptions a year are written in the UK. Of these, 50% are given to patients over the age of 60 [10]. Furthermore, there has been a dramatic increase in sales of non-prescription analgesics, especially paracetamol and non-aspirin NSAIDs for the last two decades. However, NSAIDs are also well recognised as a cause of serious, indeed even life-threatening adverse events. The most common side effects are gastrointestinal (GI) adverse events that range from non-ulcer dyspepsia to symptomatic gastroduodenal ulcers, ulcer bleeding and perforation.

In the 1970s, inhibition of PG synthesis mediated by the COX enzyme was shown to be the major mechanism underlying both the therapeutic and main toxic actions of NSAIDs. In the early 1990s, COX activity was found to be associated with two distinct isoenzymes, namely COX-1 and COX-2. At that time, all available NSAIDs appeared to be non-selective COX-2 and COX-1 inhibitors at therapeutic doses. Interestingly, COX-1 is constitutively expressed and is responsible for the production of PGs involved in GI mucosal protection, whereas at sites of tissue damage, COX-2 is induced to generate prostaglandins which mediate pain and inflammation. Accordingly, coxibs were developed with the expectation that they would retain the analgesic and anti-inflammatory properties of traditional NSAIDs, while being less toxic to the GI tract. These promises came to fruition; but there were mixed reactions to the GI advantage of coxibs over non-selective NSAIDs because the greatest benefit of coxibs was a decreased incidence of endoscopic ulcers, but not complicated ulcers [11].

In the early 2000s, placebo-controlled trials established that rofecoxib, celecoxib and valdecoxib were associated with an increased risk of serious vascular events, especially myocardial infarction (MI) [12]. Therefore, a worldwide withdrawal of rofecoxib was announced by Merck & Co. on 30 September 2004. Valdecoxib was withdrawn from the market in 2005 because of an increased risk of serious skin reactions in addition to concerns about its cardiovascular safety [12]. Although it is generally accepted that the cardiovascular hazard of coxibs is a class effect, conventional NSAIDs may also have the potential for causing atherothrombotic complications, possibly by inducing an increase in systolic blood pressure [12]. In fact, the FDA requires that all NSAIDs carry a black-box warning on the package insert advising patients of the potential increased cardiovascular risk [101]. In contrast, the European Medicines Agency (EMEA) has required labelling of coxibs only, while acknowledging that '*it cannot be excluded that non-selective NSAIDs may be associated with a small increase in the absolute risk for thrombotic events, especially when used at high doses for long-term treatment*' [102]. Interestingly, a meta-analysis of published and unpublished tabular data from randomised trials indicated that compared with placebo, coxibs are associated with a 1.42-fold increased risk of serious vascular events, defined as MI, stroke or vascular death (95% confidence interval [CI]: 1.13 – 1.78) [13]. In other words, coxibs may be associated with 3 – 5 extra people having a vascular event per 1000 treated per year [13]. Furthermore, high dose regimens of diclofenac and ibuprofen, but not high-dose naproxen, appeared to be associated with an excess risk of atherothrombosis similar to that of coxibs [13]. A further major finding of this meta-analysis was that it exists as intra-class toxicity variability among non-selective NSAIDs [13]. Whether coxibs are also a non-uniform group of drugs, cannot be

dismissed [12]. Thus, the safety profile of any compound must be assessed on its individual data [12,13].

New classes of anti-inflammatory and analgesic agents are under development, including COX-inhibiting nitric oxide (NO) donators (e.g., AZD-3582) and dual 5-lipoxygenase/COX inhibitors (e.g., licofelone). Both were expected to protect the GI tract [14,15]. Furthermore, dual inhibitors that block both PG and leucotriene synthesis were hoped to have enhanced anti-inflammatory effects [15]. However, whether these two types of drugs might represent safe and effective alternatives to coxibs or conventional NSAIDs is questionable. A 6-week clinical trial undertaken in patients with OA showed that the incidence of gastroduodenal ulcers for AZD3582 was not significantly less than for naproxen, and both were higher than for placebo [14]. Similarly, there is no clinical evidence that licofelone would be more effective and/or better tolerated than the presently available NSAIDs [15].

3. Introduction to lumiracoxib

Coxibs, like non-selective NSAIDs, might exhibit different adverse experience profiles as a result of differences in relative selectivity and potency as a COX-2 inhibitor, PG-independent pharmacological properties, chemical structure and pharmacokinetic characteristics [12]. This feature, combined with marked inter-patient variability in the clinical response to individual coxibs, supports the overall rationale for the development of new compounds. Lumiracoxib (Prexige®, Novartis Pharma), a second generation coxib, is a highly selective COX-2 inhibitor with a novel chemical structure and a relatively short plasma elimination half-life ($t_{½}$) [16].

4. Chemistry

In contrast with other coxibs, lumiracoxib, 2-[2-fluoro-6-chlorophenyl]-amino-5methyl-benzeneacetic acid, lacks a sulfur-containing moiety, but possesses a carboxylic acid group, making it weakly acidic (pKa 4.7). Its molecular phenylacetic structure represents an analogue of diclofenac [16].

5. Pharmacodynamics

The human whole-blood assay using thromboxane B_2 (TXB_2) production during clotting (as an index of COX-1 activity) and PGE_2 production in response to bacterial endotoxin (as an index of COX-2 activity) has become the reference system for establishing the selectivity of NSAIDs towards COX isoforms *in vitro* [17]. Furthermore, it allows the assessment of COX-1/COX-2 selectivity after drug administration (*ex vivo*), and thereby, it is informative of what may actually happen *in vivo* at therapeutic plasma concentrations [17].

In vitro, lumiracoxib demonstrated a 400- to 515-fold preference for inhibition of COX-2 as opposed to COX-1 [17,18]. Moreover, 100% inhibition of COX-2 was achieved at a lumiracoxib concentration (1μM) that produced no inhibition of platelet COX-1 activity [18]. *Ex vivo* studies generated similar data [17-20]. Compared with placebo, lumiracoxib, at doses ≤ 300 mg b.i.d. for 9 days, did not alter ADP/collagen-induced platelet aggregation in healthy male subjects, confirming its platelet COX-1 sparing properties *in vivo* [19].

However, *ex vivo* studies showed that lumiracoxib, at least at supratherapeutic dose regimens, may affect COX-1 dependent gastric mucosal PGE_2 synthesis [20]. Lumiracoxib, at a dose of 800 mg/day for 1 week, had no significant effect on platelet COX-1 activity (-24%; 95% CI = -44 to 4%) but resulted in a significant reduction in gastric PGE_2 production (29%; 95% CI = 10 – 45%) in healthy volunteers [20]. Nevertheless, the extent to which gastric PGE_2 and TXB_2 were reduced was significantly greater with naproxen 500 mg b.i.d. (69%; 95% CI = 61 – 76%, and 97%; 95% CI = 96 – 98%) than with lumiracoxib 800 mg [20]. Conversely, lumiracoxib demonstrated similar potency to naproxen as a COX-2 inhibitor (77%; 95% CI = 65 – 85%, and 66%; 95% CI = 47 – 78%, respectively) [20].

Efficacy of lumiracoxib was found to be dose-dependent in rat models of pyresis, hyperalgesia and inflammation [18]. In these models, which have served as standard tools in the development of NSAIDs, lumiracoxib at doses well below those needed to inhibit COX-1 provided the same degree of efficacy as diclofenac in reducing fever, pain and inflammation while being less ulcerogenic [18]. Experimental evidence suggests that the anti-nociceptive effects of NSAIDs, including lumiracoxib, may involve both peripheral and central sites of action [21]. The anti-hyperalgesic effect of lumiracoxib may result from an interaction with the spinal serotoninergic system and an activation of the NO-cyclic GMP-K^+ channel pathway, besides the inhibition of COX-2 mediated PG synthesis [21].

6. Pharmacokinetics and metabolism

Lumiracoxib is rapidly absorbed following oral administration, with a peak plasma concentration (C_{max}) occurring ~ 2 h postdose [16,22]. Its bioavailability averages 74% because of a modest first-pass metabolism [22,23]. In plasma, lumiracoxib is highly bound to albumin (≥ 98%) [22,24]. The apparent plasma clearance for lumiracoxib is 8.36 l/h, and its $t_{½}$ is in the range of 3 – 6 h [19,22,23]. Lumiracoxib displays dose-proportional and time-independent pharmacokinetics at doses of ≤ 800 mg/day [19,22,23,25].

In fact, the area under the concentration-time curve (AUC) and C_{max} values increased proportionally with doses, and no accumulation of drug in plasma was noted after 12 – 91 days of continuous treatment [19,22-25]. According to a study undertaken in 52 patients with OA aged 60 ± 9 years and weighing 80 ± 17 kg, who were given lumiracoxib 100 – 400 mg/day for 4 weeks, the AUC was not significantly influenced by age, sex and body weight [25]. Moreover, the pharmacokinetic profile of

lumiracoxib does not appear to be altered by moderate hepatic impairment (Child-Pugh score: 7 – 9) [22].

The steady-state pharmacokinetics of lumiracoxib in both plasma and synovial fluid were investigated in patients with rheumatoid arthritis who received lumiracoxib 400 mg/day for 1 week [24]. On day 7, the mean trough concentration of lumiracoxib in synovial fluid (454 µg/l) was approximately three times higher than the respective mean value in plasma (155 µg/l) [24]. Following the final dose, the concentrations were initially higher in plasma than in synovial fluid; the reverse was observed from 5 h after administration until the end of the 28-h assessment period [24]. As the synovial compartment is the major site of action of NSAIDs in arthritis, the kinetics of distribution of lumiracoxib in synovial fluid are likely to extend the therapeutic action of the drug beyond that expected from plasma pharmacokinetics [24]. Finally, these data support the use of lumiracoxib in a once-daily regimen for the treament of arthritis [24].

Lumiracoxib is extensively metabolised by the hepatic CYPP450 isozyme CYP2C9 before excretion via faeces and urine in approximately equal proportions [23]. Only the 4´-hydroxy derivative has been shown to be active, having similar potency and COX-2 selectivity to the parent molecule [23]. As plasma exposure to 4´-hydroxy-lumiracoxib is ~ 10% that of the parent compound, this metabolite is unlikely to contribute significantly to efficacy [23,24].

In view of the metabolic pathway of lumiracoxib, the potential of clinically significant drug–drug interactions with other CYP2C9 substrates exists. In this respect, lumiracoxib 400 mg/day for 5 days had no significant effects on steady-state plasma *R*- and *S*-warfarin pharmacokinetics, and caused only a small increase in prothrombin time (2.4 s) compared with placebo (0.1 s) [26]. Nonetheless, in accordance with common practice, routine monitoring of coagulation is recommended when oral anticoagulants are co-administered with lumiracoxib [26]. A modest but not clinically relevant increase (18%) of mean AUC of lumiracoxib was observed in healthy subjects receiving fluconazole, a potent CYP2C9 inhibitor, suggesting that no dose adjustment of lumiracoxib is required when it is co-administered with any CYP2C9 inhibitor, including omeprazole [27,28]. The bioavailability of lumiracoxib was not affected when given with an aluminium hydroxide/magnesium hydroxide antacid [28]. Lumiracoxib 400 mg/day had no significant effect on the pharmacokinetics of low-dose methotrexate (≤ 15 mg) [29] and of either steroid hormone component of a triphasic oral contraceptive ethinyl estradiol/levonorgestrel [30]. Furthermore, lumiracoxib did not alter the efficacy of the contraceptive [30]. As with with all NSAIDs, lumiracoxib may have clinically significant pharmacokinetic and/or pharmacodynamic interactions with other drugs, including lithium, diuretics, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II antagonists, ciclosporin or tacrolimus. On the other hand, lumiracoxib, unlike ibuprofen, did not appear to undermine the antiplatelet effects of low-dose aspirin [31].

7. Clinical efficacy

7.1 Osteoarthritis

The first nine efficacy studies of lumiracoxib in symptomatic OA have been outlined in a review article [32], and some of these have already been published as an extended report [33-37]. These studies varied in duration from 1 to 52 weeks. All were randomised, double-blind, parallel-group, controlled trials, conducted in patients with primary OA of the knee and/or hip (eight studies) and hand (one study) requiring chronic NSAID therapy [32]. At baseline, OA pain intensity in the target joint was generally required to be ≥ 40 mm on a 100 mm visual analogue scale (VAS). Furthermore, patients underwent a washout period (2 – 7 days) for previous NSAIDs or analgesics prior to randomisation. Primary efficacy variables included OA pain intensity in the target joint (100-mm VAS), where in most studies, patients rated i) their worst pain experienced within the previous 24 h, ii) their global assessment of disease activity, as well as iii) assessment of pain, stiffness and physical function, using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC™) for OA of the hip and knee, and the Australian/Canadian Osteoarthritis Hand Index (AUSCAN) for OA of the hand. As such, lumiracoxib, at all doses tested (100 – 400 mg/day), provided analgesic effects and improvements in physical function, with efficacy consistently better than placebo and similar to that of its active comparators (diclofenac 150 mg/day, celecoxib 200 mg/day and rofecoxib 25 mg/day) [32]. Furthermore, lumiracoxib may have a rapid onset of action, as exemplified by an analgesic effect significantly superior to placebo as early as three hours following the first dose in patients with OA of the knee [33].

A dose-ranging study compared the efficacy of lumiracoxib 50, 100 or 200 mg b.i.d. and 400 mg once daily with placebo and the maximum therapeutic dose of diclofenac (75 mg b.i.d.) over 4 weeks in 583 adults suffering from knee or hip OA [34]. All doses of lumiracoxib were significantly superior to placebo and comparable with diclofenac in reducing pain intensity in the target joint at study end (primary efficacy criterion) [34]. In this respect, treatment–placebo differences in least-square means at week 4 were -18, -17.4, -19.1 and -23 mm for lumiracoxib 50, 100 or 200 mg b.i.d. and 400 mg/day, respectively [32]. Interestingly, there was a significant relief in pain from week 1 (first clinic visit after the start of treatment) onwards in all active treatment groups compared with placebo [34]. Furthermore, all lumiracoxib treatment regimens demonstrated comparable efficacy to each other [34]. Similar results were obtained regarding the effects of the various doses of lumiracoxib on stiffness, physical function, and patient's global assessment of disease activity [34]. A further 4-week placebo-controlled study demonstrated the efficacy of lumiracoxib 100 mg once/day in relieving the signs and symptoms of OA of the knee or hip [32].

Two 13-week Phase III trials were carried out to compare lumiracoxib 200 or 400 mg/day with placebo and celecoxib

200 mg/day in patients with OA of the knee [35,36]. Both showed that the aforementioned primary efficacy variables were significantly improved from week 2 (first assessment after the start of treatment) onwards in all active treatment groups compared with placebo [35,36]. At study end, all active treatments were associated with similar improvements according to pain intensity and the WOMAC subscales and total scores [32]. These findings were reinforced by a prespecified pooled analysis of data from participants (n = 3302) in these two studies [32]. Estimated differences in least-square means between lumiracoxib 200 mg (n = 949) and 400 mg (n = 954) and placebo (n = 474) at week 13 were -6.8 and -8.4 mm, respectively, for OA pain intensity, -8 and -9.1 mm, respectively, for patient's global assessment of disease activity, and -6.1 and -6.3 mm, respectively, for WOMAC™ total score [32]. Thus, the magnitude of improvement was similar for both doses of lumiracoxib [32]. Non-inferiority of lumiracoxib 200 mg/day to celecoxib 200 mg/day was also demonstrated [32].

A 39-week, randomised, double-blind, extension of the 13-week study by Tannenbaum *et al.* [35] showed that the efficacy of lumiracoxib 200 or 400 mg/day or celecoxib 200 mg/day was maintained during the extension phase [32]. Radiographic monitoring during this 52-week study did not demonstrate any significant difference between lumiracoxib and celecoxib with respect to joint space width [32]. For both drugs, changes in joint space width were in the range reported for natural OA disease progression, suggesting that these compounds have no deleterious effect on articular cartilage [32].

As most side effects of NSAIDs are dose-related, these drugs have been recommended to be prescribed at the minimal effective dose [12]. As already mentioned, short-term trials (1 – 4 weeks) demonstrated the efficacy of lumiracoxib 100 mg/day in symptomatic OA [32,34]. Two 13-week, randomised, double-blind clinical trials conducted in patients with OA of the knee confirmed that lumiracoxib 100 mg once/day and lumiracoxib 100 mg once/day with a loading dose of 200 mg/day for the first 2 weeks provided effective, sustained pain relief, and significant functional improvement compared with placebo [38,39]. There were no significant differences in efficacy between the two lumiracoxib groups, including at week 2, the only assessment time point at which the two groups were receiving different doses of lumiracoxib [38]. In addition, lumiracoxib was comparable to celecoxib 200 mg/day [38,39]. Whether the statistically significant improvements observed in these two studies translate into clinically significant improvements can been assessed by using the concepts of: i) minimal clinically important improvement (MCII), defined as the smallest change in a measure that signifies an important improvement in a patient's symptom score, and ii) patient acceptable symptom state (PASS), defined as the symptom score beyond which patients consider themselves well [40,41]. A patient with OA of the knee may be considered a responder by MCII if his/her changes from baseline were ≥ 19.9 mm for pain intensity (100-mm VAS), ≥ 6.19 for WOMAC function subscale (0 – 68) and ≥ 18.3 mm for patient's global assessment of disease activity (100-mm VAS) [40,42]. The corresponding PASS thresholds have been reported to be ≤ 32.3 mm, ≤ 21.1 and ≤ 32 mm, respectively [41,42]. A pooled analysis from data taken from the above two 13-week studies showed that high proportions of patients with symptomatic OA of the knee, who were treated with lumiracoxib 100 mg once/day, 'felt better' (as assessed by MCII) or 'felt good' (as assessed by PASS) (Table 1) [42]. Furthermore, lumiracoxib 100 mg/day showed clinically comparable efficacy to celecoxib 200 mg/day (Table 1) [42].

7.2 Acute pain

7.2.1 Postoperative pain

The analgesic properties of lumiracoxib in postoperative pain were first evaluated in patients experiencing moderate-to-severe pain after removal of at least two impacted third molars [43,44]. A randomised, double-blind study compared single-dose lumiracoxib 100 mg (n = 51) and 400 mg (n = 50), ibuprofen 400 mg (n = 51) and placebo (n = 50) [43]. Pain intensity was assessed by means of a four-point categorical scale, and the primary outcome measure was pain intensity difference (PID) from baseline to scheduled timepoints ≤ 12 h postdose. Lumiracoxib 400 mg and ibuprofen were superior to placebo from 1 to 12 h, whereas lumiracoxib 100 mg was superior from 1.5 to 9 h. Moreover, lumiracoxib 400 mg demonstrated the fastet median time to onset of analgesia (37.4 min) followed by ibuprofen (41.5 min), lumiracoxib 100 mg (52.4 min) and placebo (≥ 12 h). Finally, patients rated lumiracoxib 400 mg superior to the two other active comparators [43]. These findings were confirmed by a prespecified pooled analysis of two similar clinical trials that compared lumiracoxib 400 mg with rofecoxib 50 mg, celecoxib 200 mg and placebo [44]. The primary efficacy variable was the summed (time-weighted) PID (categorical) over the first 8 h postdose (sum of pain intensity differences [SPID-8]). As such, lumiracoxib was superior to its three comparators, and again demonstrated the fastest median time to analgesia (39.6 min) compared with rofecoxib (51 min), celecoxib and placebo (both > 12 h) [44]. Patient's global evaluation of lumiracoxib was comparable to rofecoxib and superior to celecoxib and placebo [44].

A randomised clinical trial was undertaken to evaluate the efficacy of single- and multiple-doses of lumiracoxib 400 mg once/day compared with naproxen 500 mg b.i.d. and placebo in 180 patients experiencing moderate-to-severe pain within 48 h of unilateral total hip or knee arthroplasty [45]. In the single-dose phase, pain intensity was assessed at baseline and at scheduled timepoints up to 12 h after the initial study dose. Lumiracoxib and naproxen were comparable and both drugs were superior to placebo for the primary efficacy measure, SPID-8 [45]. Regarding PID (categorical), lumiracoxib was statistically superior to placebo from 2 h postdose onwards, while being less effective than naproxen at early timepoints

Table 1. Mean changes from baseline and percentages of responders by MCII and PASS in patients with osteoarthritis of the knee receiving lumiracoxib 100 mg/day, celecoxib 200 mg/day or placebo for 13 weeks [42].

	Lumiracoxib 100 mg q.d. (n = 811)	Lumiracoxib 100 mg q.d. + LD (n = 805)	Celecoxib 200 mg/day (n = 813)	Placebo (n = 806)
OA pain intensity (100-mm VAS)				
• Mean (s.d.) change from baseline (mm)	-26.0 (24.8)	-26.0 (24.9)	-25.4 (25)	-19.8 (24.8)
• Responders by MCII (%)	59.7	60.7	57.0	48.8
• Responders by (PASS) (%)	43.3	45.3	42.2	35.5
WOMAC functional subscale (0 – 68)				
• Mean (s.d.) change from baseline	-11.2 (12.7)	-11.2 (12.7)	-10.5 (12.4)	-7.2 (12.6)
• Responders by MCII (%)	62.7	62.0	60.5	47.1
• Responders by (PASS) (%)	41.6	41.4	38.7	29.5
Patient's global assessment of disease activity (100-mm VAS)				
• Mean (s.d.) change from baseline (mm)	-24.2 (25.8)	-23.2 (25.6)	-21.3 (26.8)	-16.3 (25.2)
• Responders by MCII (%)	57.3	56.6	53.1	44.3
• Responders by (PASS) (%)	42.8	43.9	39.5	31.6

LD: Loading dose for the first 2 weeks; MCII: Minimal clinically important improvement; OA: Osteoarthritis; PASS: Patient acceptable symptom state; s.d.: Standard deviation; VAS: Visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

(1, 2 and 3 h) [45]. The median time to onset of analgesia was 1.54 h for the lumiracoxib group compared with 1.03 h for the naproxen group and > 12 h for the placebo group [45]. Both active drugs were generally similar and also superior to placebo during the multiple-dose phase (≤ 96 h) [45].

In summary, lumiracoxib 400 mg/day provides rapid, effective and sustained relief from postoperative pain. Overall, its efficacy is comparable with that of standard doses of non-selective NSAIDs with well-established analgesic activity.

7.2.2 *Primary dysmenorrhoea*

Two double-blind, placebo- and active-controlled, three-way crossover studies were conducted to evaluate the efficacy of lumiracoxib in women with primary dysmenorrhoea [46]. Both trials were of similar design. Eligible subjects were randomised to one of six treatment sequences, such that each subject was to receive the three treatments in three consecutive menstrual cycles. Patients were given either lumiracoxib 400 mg once/day, rofecoxib 50 mg once/day and placebo (study 1; n = 84); or lumiracoxib 400 mg once/day, naproxen 500 mg b.i.d. and placebo (study 2; n = 99). Medication was administered for ≤ 3 days starting at the onset of moderate-to-severe menstrual pain. Pain intensity was assessed using a four-point categorical scale. For the primary end point (SPID-8 after the first dose of a treatment period), all active treatments were significantly superior to placebo in each study, and lumiracoxib was comparable to rofecoxib and naproxen [46]. Overall, lumiracoxib had a similar analgesic profile to both rofecoxib and naproxen, with very similar proportions of patients rating these three drugs as 'good' or 'excellent' [46]. In addition, lumiracoxib was found to be effective at a dose of 200 mg/day for the short-term management of acute pain associated with primary dysmenorrhoea [Novartis Pharma, data on file] and is registered in a number of countries with this posology.

7.2.3 *Headache*

Paracetamol and NSAIDs are the mainstays of treatment for episodic tension-type headache, the most frequently occurring type of headache. Desirable attributes of an effective analgesic in this condition include a rapid time to onset of analgesia and the provision of significant pain relief associated with minimal side effects [47]. Single doses of lumiracoxib were shown to meet these criteria according to the results of a randomised, double-blind, placebo-controlled study [47]. The median times to onset of analgesia (primary efficacy variable) seen for lumiracoxib 200 mg (46.8 min; 95% CI = 41.2 – 51.9 min) and 400 mg (40.8 min; 95% CI = 36 – 48.1 min) were superior to placebo (> 3 h), and comparable with each other [47]. Similarly, both doses of lumiracoxib were significantly superior to placebo for all secondary efficacy end points, including SPID-3 and patient's global evaluation of treatment effects. In this respect, significantly greater proportions of patients rated treatment as 'good' or 'excellent' for lumiracoxib 200 mg (76.7%) or 400 mg (81.7%) compared with placebo (33.4%) [47].

8. Safety and tolerability

Lumiracoxib was generally well tolerated according to pooled analyses of data from the first 15 Phase II – III randomised studies in the lumiracoxib clinical development programme (Table 2) [48,49]. These comprised 11 efficacy studies in

patients with OA (n = 8) or rheumatoid arthritis (n = 3) and 4 safety sudies, ranging from 1 to 52 weeks in duration. Data from the four following treatment groups were included in the analysis: placebo, non-selective NSAIDs (diclofenac 150 mg/day, naproxen 1000 mg/day or ibuprofen 2400 mg/day), lumiracoxib 200 or 400 mg/day, and other coxibs (celecoxib 200 or 400 mg/day or rofecoxib 25 mg/day). The rate of study completion was similar across the pooled treatment groups [48]. However, discontinuations as a result of any adverse events or GI adverse events were significantly reduced in patients taking lumiracoxib or another coxib compared with non-selective NSAIDs [48]. The incidence of symptomatic upper GI tract ulcers and ulcer complications (GI perforation, obstruction and bleeding) was reduced nearly 10-fold with lumiracoxib (1.7 events per 100 patient-years; 95% CI = 1.1 – 2.4) and other coxibs (1.4 events per 100 patient-years; 95% CI = 0.7 – 2.6) compared with non-selective NSAIDs (13.7 events per 100 patient-years; 95% CI: 9.5 – 18.8) [48]. Furthermore, dyspepsia and upper abdominal pain were reported by 16.8 and 11.6% of patients receiving conventional NSAIDs, respectively. These were reduced by ~ 50% with lumiracoxib (8.7 and 4.7%, respectively) and other coxibs (10.4 and 5.1%, respectively) [48]. Finally, lumiracoxib compared favourably with conventional NSAIDs and was comparable with other coxibs with respect to sodium/fluid retention, as indicated by the incidence of oedema, body weight gain and blood pressure increase in patients with or without hypertension at baseline [49].

However, these findings derived from data of studies that were primarily oriented toward efficacy. Thus, they needed to be validated by adequate studies dealing firstly with safety.

8.1 Endoscopic studies

The ulcerogenic potential of lumiracoxib was first assessed by using upper GI endoscopic investigations. Two 8-day, randomised, double-blind, placebo-controlled, endoscopic studies evaluated the GI tolerability of lumiracoxib 400 or 800 mg/day and naproxen 1000 mg/day in healthy subjects. No subjects developed gastroduodenal erosions or ulcers in the lumiracoxib group (n = 44) compared with > 65% subjects in the naproxen group (n = 44) [20,50]. In these short-term studies, lumiracoxib at supratherapeutic doses appeared to exhibit a gastroduodenal safety profile similar to placebo [20,50]. Furthermore, lumiracoxib, unlike naproxen, did not affect small and large bowel permeability as assessed by using the [^{51}Cr]-EDTA method [20].

A 13-week, double-blind endoscopic study compared the gastroduodenal safety of lumiracoxib 200 mg/day (n = 264) or 400 mg/day (n = 260) with ibuprofen 2400 mg/day (n = 260) and celecoxib 200 mg/day (n = 258) in patients with OA who had virtually normal gastroduodenal and oesophageal mucosae at entry to study [51]. The majority of patients were female (76.7%) with a mean age of ~ 58 years. The proportion of patients positive for *Helicobacter pylori* was between 65.5% (celecoxib group) and 72.7% (lumiracoxib 400-mg group). The cumulative incidence of gastroduodenal ulcers ≥ 3 mm in diameter at study end (primary end point) was significantly lower in the lumiracoxib 200-mg (4.3%) and 400-mg (4%) groups than in the ibuprofen group (15.7%), and was similar to the celecoxib group (3.2%). This incidence was not influenced by *H. pylori* status in any treatment group. Interestingly, the cumulative incidence of gastroduodenal ulcers ≥ 5 mm (a size that seems to be more clinically relevant) showed a similar pattern (3.9, 3.6, 12.5 and 2.8%, respectively). Compared with patients receiving ibuprofen, fewer patients receiving lumiracoxib or celecoxib experienced adverse GI symptoms. Accordingly, the percentage of patients requiring antacid rescue medication was 89.1% in the ibuprofen group versus 84.7 and 83% in the lumiracoxib 200-mg and 400-mg groups, respectively, and 84.6% in the celecoxib group. Finally, early discontinuation related to any adverse event was more frequent with ibuprofen (13.5%) than with lumiracoxib 200 mg (7.6%) or 400 mg (5.4%) and celecoxib (6.2%) [51]. A similar endoscopic study that compared lumiracoxib 400 or 800 mg/day with ibuprofen 2400 mg/day and celecoxib 200 mg/day in 893 patients with rheumatoid arthritis yielded similar results [52].

As the correlation between endoscopic ulcers and clinical outcomes is debated, it is imperative that a decrease in symptomatic ulcers and ulcer complications be shown before establishing the GI safety of an NSAID.

8.2 Outcome study

The TARGET (Therapeutic Arthritis Research and Gastrointestinal Event Trial), was a large study performed to test the hypothesis that patients receiving supratherapeutic doses of lumiracoxib would have a lower risk of upper GI ulcer complications than those receiving standard doses of conventional NSAIDs [53]. TARGET enrolled 18,325 patients with OA who were ≥ 50 years of age. It was a 52-week, randomised investigation, using parallel group methodology, and consisted of two similarly sized substudies with identical design. One compared lumiracoxib 400 mg/day with ibuprofen 800 mg t.i.d. and the other compared lumiracoxib 400 mg/day with naproxen 500 mg b.i.d. Within each substudy, randomisation was stratified by age and low-dose aspirin use. Individuals taking gastroprotective drugs and those with an active upper GI ulceration in the previous month, upper GI bleeding in the past year, or any history of gastroduodenal perforation or obstruction were excluded from enrolment. Patients with a history of MI, stroke, coronary-artery bypass graft, invasive coronary revascularisation, new-onset angina within the previous 6 months or electrocardiogram evidence of recent silent myocardial ischaemia were also excluded, as were those with severe congestive heart failure and those receiving anticoagulation therapy. Conversely, patients at increased risk for coronary heart disease were eligible for study entry, provided that they had been taking low-dose aspirin for ≥ 3 months before randomisation. The primary end point was difference in

Table 2. Pooled analysis of data from the first 15 Phase II – III randomised studies in the lumiracoxib clinical program [48].

	Placebo (n = 1860)	Conventional NSAIDs* (n = 981)	Lumiracoxib‡ (n = 5432)	Other coxibs§ (n = 2168)
Patients mean (s.d.) age, years	59.3 (12.1)	55.1 (11.6)	59.3 (11.9)	60.1 (11.7)
Discontinuation rates				
- any cause	26.8 %	24.6 %	22.0 %	20.2 %
- any adverse events	6.4 %	12.0 %	7.9 %	8.1 %
- GI adverse events	1.7 %	8.4 %	3.3 %	3.4 %
Severe GI adverse events¶ [number per 100 patient-years (95% CI)]	0.0	13.7 (9.5 – 18.8)	1.7 (1.1 – 2.4)	1.4 (0.7 – 2.6)
Hypertension				
- new onset hypertension	0.9 %	3.2 %	2.1 %	2.5 %
- aggravation of hypertension	0.7 %	5.3 %	1.9 %	2.1 %
Oedema	1.5 %	3.2 %	2.4 %	3.0 %
Body weight gain (≥ 5 %)	4.8 %	9.2 %	8.5 %	9.2 %

* Diclofenac 150 mg/day, naproxen 1000 mg/day or ibuprofen 2400 mg/day.
‡ 200 or 400 mg/day.
§ Celecoxib 200 – 400 mg/day or rofecoxib 25 mg/day.
¶ Symptomatic GI ulcers and ulcer complications (perforation, obstruction and bleeding).
GI: Gastrointestinal; NSAID: Non-steroidal anti-inflammatory drug; s.d.:Standard deviation.

time-to-event distribution of definite or probable upper GI ulcer complications (clinically significant bleeding, perforation or obstruction from erosive or ulcer disease). The incidence of all ulcers (uncomplicated symptomatic ulcers plus ulcer complications as defined above) was a secondary end point. A key secondary objective of TARGET was to assess the cardiovascular safety of lumiracoxib compared with ibuprofen and naproxen. In this respect, the primary outcome variable was a composite end point, as defined by the Antiplatelet Trialists' Collaboration (APTC): confirmed silent (electrocardiogram-detected) MI, confirmed or probable clinical MI, stroke (ischaemic or haemorrhagic) and cardiovascular death. Additional important safety end points included liver safety (increase of alanine or aspartate transaminase to > 3-fold the upper limit of normal, or total bilirubin value of > 51.3 µmol/l) and major renal events (doubling of serum creatinine from baseline, or proteinuria ≥ 3 g/l). Three independent safety adjudication committees were established before enrolment of patients to assess and categorise GI, cardiovascular and hepatobiliary events. As prespecified, data from the two substudies were pooled for analysis.

Treatment groups were balanced in terms of baseline characteristics (mean age: 63 years; patients ≥ 75 years: 11%; women: 76%; low-dose aspirin: 24%) and major independent cardiovascular risk factors (current smoking: 10%; hypertension ~ 45%; diabetes ~ 8%; dyslipidaemia: 20%). However, the lumiracoxib versus naproxen substudy included more patients with a previous history of vascular risk and evidence of *H. pylori* infection than the the lumiracoxib versus ibuprofen substudy (12 versus 8, and 47 versus 41%, respectively).

The main results of TARGET are shown in Tables 3 and 4. When the overall population was considered, upper GI ulcer complications were reduced to about a third with lumiracoxib compared with ibuprofen or naproxen (hazard ratio = 0.34; 95% CI = 0.22 – 0.52). However, for patients taking low-dose aspirin, there was no evidence of such a benefit, as the incidence of these events was virtually identical for lumiracoxib and the comparator NSAIDs (hazard ratio = 0.79; 95% CI = 0.4 – 1.55) [53].

The incidence of the primary cardiovascular end point was low in this population. It did not differ between treatment groups (lumiracoxib 0.65 versus comparator NSAIDs 0.55%) or when analysed by aspirin use for cardiovascular prophylaxis, age or sex [54]. No significant difference between the combined non-selective NSAIDs and lumiracoxib groups was recorded in rates (clinical or silent) of confirmed or probable MIs or stroke (Figure 1) [54]. In the lumiracoxib versus naproxen substudy, there was a non-statistically significant excess of both APTC end point and MIs with lumiracoxib (n = 40 [0.84%] and n = 18 [0.38%], respectively) compared with naproxen (n = 27 [0.57%] and n = 10 [0.21%], respectively), the corresponding hazard ratio being 1.46 (95% CI = 0.89 – 2.37) and 1.77 (95% CI = 0.82 – 3.84), respectively [54]. Conversely, in the second substudy, the incidence of the APTC end point was numerically lower in the lumiracoxib group (0.43%) than in the ibuprofen group (0.52%), with a hazard ratio of 0.76 (95% CI = 0.41 – 1.40) [54]. Regarding congestive heart

Table 3. Number and incidence of upper GI and cardiovascular complications and discontinuation due to adverse events in TARGET.

	Substudy 1		Substudy 2		Both studies	
	Lumiracoxib n = 4376	***Ibuprofen*** n = 4397	***Lumiracoxib*** n = 4741	***Naproxen*** n = 4730	***Lumiracoxib*** n = 9117	***NSAIDs*** n = 9127
Upper GI complications						
- overall population	10 (0.23 %)	33 (0.75 %)	19 (0.40 %)	50 (1.06 %)	29 (0.32 %)	83 (0.91 %)
- non-aspirin population	5/3401 (0.15 %)	18/3431 (0.82 %)	9/3549 (0.25 %)	36/3537 (1.02 %)	14/6950 (0.20 %)	64/6968 (0.92 %)
- aspirin population	5/975 (0.51 %)	5/966 (0.52 %)	10/1192 (0.84 %)	14/1193 (1.17 %)	15/2167 (0.69 %)	19/2159 (0.88 %)
Cardiovascular complications						
- total number	33 (0.75 %)	32 (0.73 %)	52 (1.10 %)	43 (0.91%)	85 (0.93 %)	75 (0.82 %)
- primary endpoint	19 (0.43 %)	23 (0.52 %)	40 (0.84 %)	27 (0.57 %)	59 (0.65 %)	50 (0.55 %)
- MI	5 (0.11 %)	7 (0.16 %)	18 (0.38 %)	10 (0.21 %)	23 (0.25 %)	17 (0.19 %)
Discontinuation due to adverse events						
- total number	699 (16 %)	789 (18 %)	710 (15 %)	848 (18 %)	1409 (15 %)	1635 (18 %)

Adapted from [16].

GI: Gastrointestinal; MI: Myocardial infarction; NSAID: Non-steroidal anti-inflammatory drug; TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial.

Table 4. Incidence of important safety endpoints in TARGET.

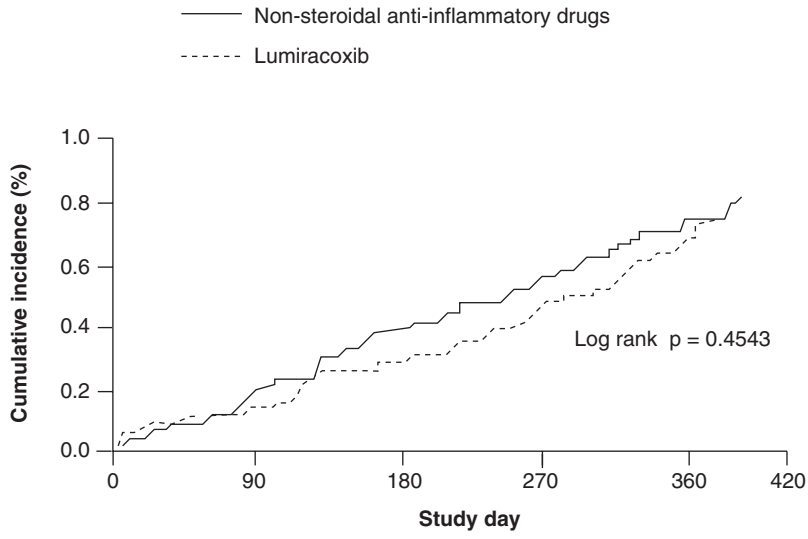
	Lumiracoxib (n = 9117)	NSAIDs (n = 9127)	Hazard ratio (95 % CI)	p Value
Upper GI complicated ulcers				
- overall population	0.32%	0.91%	0.34 (0.22 – 0.52)	< 0.0001
- non-aspirin population	0.20%	0.92%	0.21 (0.12 – 0.37)	< 0.0001
- aspirin population	0.69%	0.88%	0.79 (0.40 – 1.55)	0.4876
Symptomatic uncomplicated ulcers	0.64%	1.13%	0.55 (0.40 – 0.76)	0.0003
Cardiovascular events				
- primary endpoint	0.65%	0.55%	1.14 (0.78 – 1.66)	0.5074
- MI	0.25%	0.19%	1.31 (0.70 – 2.45)	0.4012
- stroke	0.26%	0.23%	1.11 (0.62 – 1.99)	0.7372
Abnormal liver function tests	2.57%	0.63%	3.97 (2.96 – 5.32)	< 0.0001
Major renal events	0.51%	0.37%	1.34 (0.86 – 2.10)	0.1971

Adapted from [16].

GI: Gastrointestinal; MI: Myocardial infarction; NSAID: Non-steroidal anti-inflammatory drug; TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial.

failure, its incidence was comparable in the lumiracoxib and the comparator NSAIDs groups (0.22 and 0.34%, respectively; p = 0.27) [54]. For systolic and diastolic blood pressure, least square mean changes from baseline were +0.4 and -0.1 mmHg, respectively, for lumiracoxib, compared with +2.1 and +0.5 mmHg, respectively, for comparator NSAIDs (p < 0.0001) [54].

A significantly higher proportion of patients receiving lumiracoxib had liver-function test abnormalities compared with non-selective NSAIDs (hazard ratio = 3.97; 95% CI = 2.96 – 5.32) [53]. However, these abnormalities resolved on cessation of treatment. Furthermore, clinical hepatitis was quite rare whatever the drug used: six cases were adjudicated to lumiracoxib (0.07%), two to ibuprofen



Number at risk

Lumiracoxib	9117	8110	7058	6323	5724
Non-steroidal anti-inflammatory drugs	9127	7843	6735	6045	5476

Figure 1. Incidence of composite cardiovascular end point (confirmed or probable events) in TARGET. Reproduced from [54] (figure 2 of the article by Farkouh *et al.*).

(0.05%) and one to naproxen (0.02%) [53]. In addition, major renal events did not differ between patients randomised to lumiracoxib (0.51%) and conventional NSAIDs (0.37%) [53].

Finally, the cardiovascular safety profile of lumiracoxib was assessed by meta-analysis of all randomised controlled trials of ≥ 1 week and up to 1 year in duration that were conducted in patients with OA and rheumatoid arthritis by December 2004 [55]. This analysis included 22 studies, including TARGET. Parameters analysed were the APTC composite end point, MI alone and stroke alone. This meta-analysis of 34,668 patients found no evidence that lumiracoxib was associated with a significant increase in cardiovascular risk compared with placebo, naproxen or all comparators (placebo, naproxen, diclofenac, ibuprofen, celecoxib and rofecoxib) [55].

9. Regulatory affairs

Initial approval for lumiracoxib in Europe was granted in the UK (September 2003). Subsequently, the UK acted as the reference state in the mutual recognition procedure (MRP) in the EU. However, the company decided to withdraw its licensing application pending the EMEA review on the safety of all coxibs which followed the withdrawal of rofecoxib in September 2004. Lumiracoxib was then launched in the UK (December 2005), where it has been indicated for i) the symptomatic treatment of OA (at a recommended dose of 100 mg once/day), ii) short-term management of acute pain associated with primary dysmenorrhea (at a recommended dose of 200 mg/day for a maximum of 3 days per menstrual cycle) and iii) acute pain following orthopaedic or dental surgery (at a recommended dose of 400 mg once/day for a maximum of 5 days) [103].

Lumiracoxib successfully completed the MRP in November 2006 in all 26 EU member states for the symptomatic treatment of OA of the knee and hip with 100 mg once/ day dosing. In addition to the EU, lumiracoxib has already been approved in > 25 countries for OA and/or acute pain related to primary dysmenorrhoea and dental or orthopaedic surgery.

Novartis Pharma has also filed for regulatory approval of lumiracoxib in the US in November 2002. Since the FDA made a request for additional data, the company has conducted additional studies and submitted a complete response for approval in March 2007.

10. Conclusion

Lumiracoxib is a highly selective COX-2 inhibitor that differs from first generation coxibs in that it is rapidly cleared from the blood. Clinical trials provided convincing evidence that it is as effective as existing NSAIDs in reducing acute or chronic pain while having a superior GI profile compared with non-selective NSAIDs, at least in patients not taking low-dose

aspirin. Available data do not suggest that lumiracoxib is associated with an increased risk of cardiovascular thrombotic events compared with existing NSAIDs. Moreover, lumiracoxib appeared to induce a slightly smaller increase in blood pressure than conventional NSAIDs, such as ibuprofen and naproxen. Nonetheless, lumiracoxib was not shown to exhibit a pattern of nephrotoxicity differing from that of other coxibs or non-selective NSAIDs. Finally, the incidence of elevations in liver function tests but not clinical hepatitis, was higher in patients given lumiracoxib compared with those receiving ibuprofen or naproxen.

11. Expert opinion

As an analgesic, lumiracoxib was found to be as effective as standard doses of both non-selective and COX-2 selective NSAIDs. Lumiracoxib 100 mg/day was shown to provide rapid and sustained analgesia and improvement in overall function in most patients with symptomatic OA, with efficacy similar to that of diclofenac or celecoxib. Although no dose–response relationship could be demonstrated in the Phase II – III trials, it is to be expected that some people with OA would have received additional benefit by increasing the dose to 200 mg/day. Lumiracoxib 100 mg once/day remains as the only approved dose regimen in most countries. Nevertheless, in view of the inter-patient variability in the clinical response to individual NSAIDs, it is very likely that lumiracoxib will be an attractive option for patients who tried other conventional or COX-2 selective NSAIDs without success.

In other respects, lumiracoxib appeared to have an improved safety profile compared with that of non-selective NSAIDs, and its safety profile was seen to be similar to that of first generation selective COX-2 inhibitors [48,53]. Moreover, lumiracoxib resulted in a significantly lower incidence of ulcer complications compared with non-selective NSAIDs, although the absolute and relative risk reductions observed in TARGET were less impressive than anticipated from pooled analyses of Phase II – III trials. However, for patients taking low-dose aspirin, there was no evidence of such a benefit. Regarding GI adverse events, a key clinical issue that remains unsettled is whether or not lumiracoxib is safer than an anti-ulcer medication added to a non-selective NSAID. To address this question, the GI tolerability and safety of lumiracoxib should have been compared with those of a conventional NSAID combined with a proton pump inhibitor (PPI) [56]. Such a combination is often used in routine clinical practice because PPIs may offer the advantage of not only reducing NSAID-related GI ulcers, but also preventing dyspeptic symptoms (which is the most common reason for the discontinuation of any NSAID) [57]. Furthermore, present guidelines recommend the use of either a selective COX-2 inhibitor or a non-selective NSAID plus an effective gastroprotective agent, such as a PPI, in patients with increased GI risk, such as those receiving long-term NSAID therapy at high doses and/or taking low-dose aspirin [2,3].

The influence of coxibs on cardiovascular health has been much debated lately. With respect to this debate, there is no consistent evidence that lumiracoxib may be associated with an increased hazard of cardiovascular events compared with non-selective NSAIDs [54,55]. It has been argued that clinical trials, particularly TARGET, did not reflect a 'real world' OA population because patients with significant pre-existing coronary artery disease were excluded from that study [57]. However, lumiracoxib is not intended for these patients as the EMEA has contraindicated the use of all coxibs in patients with established ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease, as well as patients with congestive heart failure (New York Heart Association class II – IV). It has also been stressed that TARGET indicated a numerical but possibly clinical relevant excess of thrombotic cardiovascular events with lumiracoxib compared with naproxen [57]. However, these findings may be ascribed to the fact naproxen may exert a cardioprotective effect in some individuals [58]. Moreover, it is noteworthy that compared with lumiracoxib, ibuprofen was associated with a nonsignificant increase in thrombotic adverse events in TARGET. As increase in blood pressure may be one of the mechanisms underlying the cardiovascular thrombotic hazard associated with chronic exposure to any NSAID [12], we should point out that mean changes in blood pressure observed in TARGET, albeit modest in all treatment groups, were less pronounced for lumiracoxib than for comparator NSAIDs [54]. In total, it may be assumed that lumiracoxib, at the recommended approved dose for OA, would not carry a significant cardiovascular risk.

Finally, TARGET may raise concern about a possible hepatotoxic potential of lumiracoxib. It was hypothesised that the use of a supratherapeutic dose of lumiracoxib could have resulted in an overestimatation of the hepatotoxicity of the drug [53]. However, the risk of elevated aminotransferases associated with diclofenac, which is chemically related to lumiracoxib, did not appear to be dose-related [59]. A reassuring finding is that asymptomatic elevations in liver tests have inadequate sensitivity and specificity to predict serious clinical liver injury [59]. In any case, postmarketing surveillance should help clarify the actual risk for clinical hepatitis with lumiracoxib.

In summary, lumiracoxib has the potential to become a useful therapeutic option for many patients, particularly those who did not respond to other coxibs or non-selective NSAIDs, or did not tolerate them. To minimise the risk of adverse events, lumiracoxib, like all other NSAIDs, should be used at the lowest effective dose for the shortest time necessary to control symptoms.

Declaration of interest

F Berrenbaum is a member of the International Advisery Board committee for Novartis. He was a Principal Investigator on a clinical study with lumiracoxib. This article was independently commissioned and no fee has been received for preparation of the manuscript.

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