

Lumiracoxib: the evidence of its clinical impact on the treatment of osteoarthritis

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Abstract

Introduction: The symptoms of osteoarthritis (OA) include joint pain, stiffness, and a reduced ability to perform normal daily activities, which result in decreased quality of life. There is currently no known cure or means of preventing the progression of joint damage due to OA. Therefore, treatment focuses on the control of symptoms, including the use of various agents [including nonselective and selective nonsteroidal antiinflammatory drugs (NSAIDs)] to provide pain relief and reduce inflammation. Lumiracoxib is a selective cyclooxygenase-2 (COX-2) inhibitor for the treatment of OA.

Aims: To review the evidence for the treatment of OA with lumiracoxib.

Evidence review: There is evidence that lumiracoxib reduces the pain and stiffness associated with OA, and is as effective as nonselective NSAIDs, and the COX-2 inhibitor celecoxib. There is some evidence that lumiracoxib treatment results in a lower incidence of upper gastrointestinal (GI) ulcer complications compared with nonselective NSAIDs. However, evidence suggests that there is no GI benefit in patients receiving concomitant aspirin medication. With the exception of GI ulcers, the evidence indicates that lumiracoxib has a tolerability profile similar to nonselective NSAIDs: low risk of cardiovascular (CV) events and a low incidence of edema. Changes in liver function occur in some patients, largely at doses >100 mg. The cost effectiveness of lumiracoxib compared with nonselective NSAIDs remains to be determined.

Clinical value: Lumiracoxib is an alternative treatment option for OA which provides effective pain relief without the GI complications associated with nonselective NSAIDs, and with a low risk of CV events. Lumiracoxib is contraindicated in patients with current, previous, or at risk of, hepatic impairment.

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Key words: cardiovascular, COX-2 inhibitor, evidence, gastrointestinal, lumiracoxib, osteoarthritis, outcomes, treatment

Core evidence clinical impact summary for lumiracoxib in osteoarthritis

Outcome measure	Evidence	Implications
Patient-oriented evidence		
Reduced pain intensity	Clear	Effective relief of pain intensity, comparable with celecoxib, rofecoxib, diclofenac, naproxen, and ibuprofen
Improvement in joint stiffness	Clear	Improvement in joint stiffness (WOMAC score) comparable with celecoxib and diclofenac
Improved quality of life	Clear	Improvement in ability to perform daily activities (WOMAC score) comparable with celecoxib and diclofenac. Improvement in physical functioning and mental health (SF-36) compared with placebo
Tolerability	Clear	Minor GI adverse events are frequent (e.g. dyspepsia, diarrhea, and nausea) and occur at a similar incidence with celecoxib, diclofenac, ibuprofen, and naproxen
Low incidence of GI ulcers	Substantial	Lower risk of upper GI ulcer complications compared with ibuprofen or naproxen in nonaspirin population only
Changes in liver function	Substantial	No clinically relevant elevations in ALT/AST levels were reported at the indicated dose of lumiracoxib (100 mg) although isolated cases of liver-related adverse events have been reported at this dose. AST/ALT elevations may occur at higher doses (400 mg). Lumiracoxib should not be used in patients with, or at risk of, liver disease, and liver function should be monitored.
Reduced risk of hypertension	Limited	Lower risk of <i>de-novo</i> hypertension with lumiracoxib than naproxen. Reduced SBP and DBP with lumiracoxib compared with naproxen/ibuprofen
Low risk of CV events	Moderate (limited in patients at high risk)	Lumiracoxib has a similar CV risk profile as ibuprofen, and a similar CV profile as naproxen in patients taking aspirin. Lumiracoxib has an increased risk of CV events compared with naproxen in patients not taking aspirin

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Outcome measure	Evidence	Implications
Low incidence of edema	Substantial	Incidence similar to that with celecoxib, diclofenac, naproxen, and ibuprofen
Economic evidence		
Cost effectiveness	No evidence	Evidence required to determine whether clinical effectiveness translates into an economic benefit compared with other treatments for OA

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CV, cardiovascular; DBP, diastolic blood pressure; GI, gastrointestinal; OA, osteoarthritis; SBP, systolic blood pressure; SF, Short Form; WOMAC, Western Ontario and McMaster Universities OA Index.

Scope, aims, and objectives

Osteoarthritis (OA) is one of the most prevalent forms of arthritis. There is currently no known cure or means of preventing OA. Therefore, treatment focuses on the control of symptoms, including the use of the nonselective nonsteroidal antiinflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors. The COX-2 inhibitors were developed with the aim of providing pain relief with less gastrointestinal (GI) adverse effects than the NSAIDs. In recent years, there have been concerns regarding the cardiovascular (CV) safety of COX-2 inhibitors, and there is a need for newer agents that demonstrate a clinical benefit in a greater proportion of OA patients compared with the risk of a CV event. Lumiracoxib (Prexige®, COX-189; Novartis) is an orally active selective COX-2 inhibitor developed for the treatment of OA, rheumatoid arthritis (RA), and acute pain.

The objective of this article is to review the evidence base for the clinical use and CV risk–benefit profile of lumiracoxib in the management of patients with OA. The use of lumiracoxib in acute pain is excluded.

Methods

English language medical literature databases were searched for relevant evidence related to the treatment of OA with lumiracoxib. The searches were conducted in December 2005 using the search terms “lumiracoxib OR Prexige.” The cut-off date was from the beginning of the database to the date of the search unless otherwise stated.

- PubMed, <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>
- EMBASE, <http://datastarweb.com>
- BIOSIS, <http://datastarweb.com>
- Database of Abstracts of Reviews of Effects (DARE), <http://www.york.ac.uk/inst/crd/darehp.htm>
- Cochrane Database of Systematic Reviews (CDSR), <http://www.cochrane.org/index0.htm>
- Public Library of Science, <http://clinicaltrials.plosjournals.org/>
- Clinical Evidence (BMJ), <http://www.clinicalevidence.com>
- <http://www.clinicaltrials.gov>
- <http://www.clinicalstudyresults.org>. Search strategy “Novartis AND lumiracoxib”

- National Institute for Health and Clinical Excellence (NICE), <http://www.nice.org.uk>
- National Guideline Clearinghouse, <http://www.guideline.gov>. Search strategy “osteoarthritis”

After removal of duplicates, a total of 235 records were identified. Clinical guidelines for OA were also identified from NICE, the American College of Rheumatology (ACR), and the European League Against Rheumatism (EULAR). Records were manually reviewed and any animal studies, *in-vitro* studies, news articles, nonsystematic reviews, editorials, articles that mentioned lumiracoxib but did not discuss clinical trial data, duplicated data presented in previous publications, pharmacokinetic and interaction studies which were not directly relevant to the review, and studies with lumiracoxib in indications other than OA were excluded. Eighteen papers remained and were included in the evidence base (Table 1). Two systematic reviews were identified. All other articles were of level 2 evidence reported as full publications.

Table 1 | Evidence base included in the review

Category	Number of records	
	Full papers	Abstracts
Initial search	235	32
records excluded	217	28
records included	18	4
Search updates, new records	13	0
records excluded	7	0
records included	6	0
Level 1 clinical evidence (systematic review, meta analysis)	6	1
Level 2 clinical evidence (RCT)	12	3
Level ≥3 clinical evidence		
trials other than RCT	0	0
case reports	0	0
pharmacokinetic studies	6	0
Economic evidence	0	0
Total records included	24	4

For definition of levels of evidence, see Editorial Information on inside back cover.
RCT, randomized controlled trial.

Online abstracts from the following congresses were also searched in December, 2005 using the search terms “lumiracoxib OR Prexige”:

- ACR, all conferences from 2002 to 2005, <http://www.rheumatology.org/annual/abstracts/search.asp>
- EULAR, all conferences from 2004 to 2005, <http://www.abstracts2view.com/eular/>
- Osteoarthritis Research Society International (OARSI) 9th World Congress, December 2–5, 2004, http://www.oarsi.org/04Abstracts/Final_OARSI04_Abtracts.pdf

A total of 32 abstracts were identified (Table 1). Twenty-eight abstracts were excluded because they were animal studies ($n=3$), *in-vitro* studies ($n=1$), were in indications other than OA ($n=3$), were nonrelevant pharmacokinetic/pharmacodynamic studies ($n=2$), did not cite data ($n=1$), or were abstracts that duplicated results from OA studies which have since been published in full ($n=18$). One abstract was level 1 evidence (pooled analysis), and all other abstracts were of level 2 evidence.

PubMed searches were updated on January 27, 2006 and again on May 14, 2007. A total of 13 new records were identified, of which seven were excluded for the following reasons: *in-vivo* study ($n=1$), animal study ($n=1$), review article ($n=5$). Six articles remained, and were included (Table 1).

Disease overview

OA is the most common form of arthritis, which gradually damages the cartilage lining the joints (and the underlying bone) primarily in the hands, knees, hips, and spine. The four main risk factors for OA are age, family history, obesity, and joint trauma (WHO 2003). It is estimated that symptomatic OA affects 9.6% of men and 18% of women aged ≥ 60 years worldwide, and is more prevalent in Europe and the US than in other parts of the world (Woolf & Pfleger 2003). Of the 115.9 million US adults aged ≥ 35 years, 24.3 million (21%) have OA (Singh et al. 2002). Globally, approximately 40% of individuals over 70 years of age suffer from OA of the knee (WHO 2003).

The prevalence of OA is expected to increase due to the increasing proportion of the elderly in the population (Reginster 2002), and it is expected to be the fourth leading cause of disability by 2020 (Woolf & Pfleger 2003). The increasing burden of musculoskeletal disorders, such as OA, has been recognized by the United Nations and the World Health Organization (WHO), which has endorsed the Bone and Joint Decade 2000–2010 initiative, with the aim of increasing awareness of these conditions (Woolf & Pfleger 2003).

The symptoms of OA include joint pain, stiffness, and a reduced ability to perform normal daily activities, which result in a decreased quality of life. Approximately 80% of patients with OA have limitation of movement and 25% cannot perform their major daily activities (WHO 2003). Indeed, musculoskeletal conditions such as OA have been associated with a poorer quality of life than CV, chronic respiratory, and GI conditions (Reginster 2002).

Economic burden of OA

In the US alone, of the \$US214.9 billion in total costs for musculoskeletal disorders in 1995, \$US82.4 billion was associated with various forms of arthritis (the most prevalent being OA

and RA) (WHO 2003). In addition, the economic burden of musculoskeletal disorders in Canada has been reported to be close to that of cancer (Badley 1995).

The direct and indirect costs of OA place a considerable burden both on the individual and society. A Canadian study estimating the direct and indirect arthritis-attributable costs to individuals with disabling hip and/or knee OA demonstrated that 80% of costs incurred were for time lost from employment and leisure by the patient and unpaid informal caregivers. Costs increased with worsening health status and greater OA severity (Gupta et al. 2005). In addition, a European retrospective study in patients with OA of the knee reported that direct costs over a period of 12 months (2000–2001) were €934/patient per year (including €146 on therapy, of which 42% was spent on drugs), and indirect costs were €1236/patient per year (31% due to loss of productivity of patients and 60% due to informal care provided by primary caregivers) (Leardini et al. 2004).

Pathophysiology of OA

Prostaglandins cause the swelling and pain associated with OA (Mitchell & Warner 1999). The cyclooxygenase enzymes play a key role in the production of prostaglandins by converting arachidonic acid to prostaglandin H_2 (PGH_2), which is then metabolized by specific isomerases to tissue-specific prostanoids [e.g. PGI_2 (prostacyclin) and TXA_2 (thromboxane)] (Fig. 1). To date, two isoforms of the cyclooxygenase enzyme, COX-1 and COX-2, have been identified. COX-1 is produced constitutively in several tissues including the GI tract, endothelial cells, kidney, and platelets, whereas COX-2 is expressed constitutively in some tissues (e.g. kidney) and is also inducible (Dubois et al. 1998; Warner &

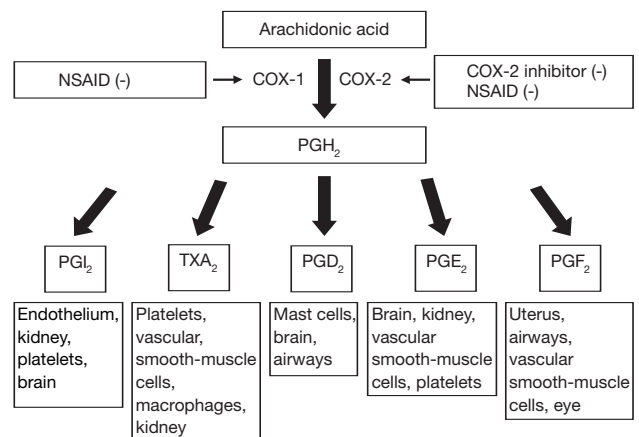


Fig. 1 | The cyclooxygenase pathway (reproduced with permission from Fitzgerald & Patrono 2001). Arachidonic acid is converted by cyclooxygenase (COX)-1 and COX-2 to the intermediate prostaglandin H_2 (PGH_2). PGH_2 is converted by tissue-specific isomerases to multiple prostanoids; prostacyclin (PGI_2), thromboxane A_2 (TXA_2), prostaglandin D_2 (PGD_2), prostaglandin E_2 (PGE_2), and prostaglandin F_2 (PGF_2). These prostanoids exert prominent effects via cell-membrane receptors

Mitchell 2004). Through its production of gastroprotective prostaglandin E₂ (PGE₂), the constituent COX-1 enzyme is recognized as being protective of the GI system. Cytokines and growth factors increase the expression of COX-2 at inflammatory sites. Therefore, the COX-2 enzyme primarily mediates pain and inflammation (Warner & Mitchell 2004).

Current therapy options

Currently, there is no known cure for OA or means of preventing it. The main goals of OA management are to control pain and to improve function and quality of life, while avoiding adverse side effects. Pharmacologic treatments for OA include: analgesics such as acetaminophen (paracetamol), which relieve pain but do not reduce inflammation; NSAIDs, which are both analgesic and antiinflammatory; injectable corticosteroids; and symptomatic slow-acting drugs for OA such as glucosamine sulfate, chondroitin sulfate, and hyaluronic acid. Nonpharmacologic treatments such as patient education, diet, exercise, and the use of insoles may also improve the symptoms of OA. Surgical treatment (i.e. prosthetic joint replacement) is generally only used when there is significant joint damage and all other treatment options have failed.

NSAIDs relieve pain and inflammation by blocking the action of the COX-2 enzyme. There are currently two types of NSAIDs: nonselective NSAIDs suppress both the COX-1 and COX-2 enzymes to varying degrees; COX-2 inhibitors (i.e. selective NSAIDs) suppress the COX-2 enzyme only (Fitzgerald & Patrono 2001).

Nonselective NSAIDs

Nonselective NSAIDs such as naproxen, ibuprofen, diclofenac, and nabumetone, have been available on the market for many years. A major disadvantage of nonselective NSAIDs is their potential to cause GI side effects by inhibition of COX-1 and topical toxicity (Lazzaroni & Porro 2004). For example, nonselective NSAIDs increase the risk of serious ulcer complications (bleeding, perforation, obstruction), hospitalization, surgery, and death (Singh et al. 1997; Wolfe et al. 1999). In the 1980s, GI complications caused by nonselective NSAID use was estimated to cause approximately 16 000 deaths and 100 000 hospitalizations each year in the US alone.

Risk factors for NSAID-associated upper GI complications include use of multiple NSAIDs (e.g. NSAID and aspirin), high doses of NSAIDs, prior ulcer complications, advanced age, and concomitant corticosteroid or anticoagulant use (Scheiman & Fendrick 2005).

Approximately 50% of patients who regularly take nonselective NSAIDs have gastric erosions, and 15–30% have ulcers when examined by endoscopy. Clinical upper GI events may occur in 3–4.5% of patients taking NSAIDs, and serious complicated events develop in approximately 1.5% (Laine 2001). These GI adverse events often lead to discontinuation of treatment, and may have an important impact on the patient's quality of life and healthcare costs. Therefore, the human and economic costs of these complications could be reduced by using medications which reduce their incidence.

In order to reduce the incidence of GI complications nonselective NSAIDs may be used in combination with gastroprotective agents such as misoprostol, H₂ receptor antagonists, and proton pump inhibitors (PPIs), which add to the total cost of therapy. But patient compliance to misoprostol is limited by its side effects (e.g. diarrhea and abdominal cramps), and H₂ receptor antagonists do not offer significant protection against gastric ulcers (Singh & Triadafilopoulos 2005). In comparison to these other treatments PPIs are better tolerated. Eradication of *Helicobacter pylori* intestinal infection has also been shown to reduce peptic ulcer incidence in patients receiving NSAIDs. However, it was less effective at preventing NSAID-associated ulcers than treatment with a PPI (Vergara et al. 2005). Evidence suggests that *H. pylori* infection and NSAID use are independent risk factors for GI complications (Huang et al. 2002).

COX-1 also plays a role in the synthesis of prostanoids which regulate renal function. It is well established that nonselective NSAIDs have adverse effects on the kidney, and may cause peripheral edema and hypertension (Gambaro & Perazella 2003). Data from two meta analyses have shown that nonselective NSAIDs increase blood pressure (BP), although the effect varied depending upon the NSAID used (Pope et al. 1993; Johnson et al. 1994). In addition, two prospective studies have recently reported conflicting data regarding the increased risk of hypertension with the use of nonselective NSAIDs. A study in women demonstrated an increased risk of hypertension with high daily doses of acetaminophen and ibuprofen (Forman et al. 2005). In contrast, a study in men did not demonstrate an increased risk with these drugs (Kurth et al. 2005).

There is limited evidence that nonselective NSAIDs are associated with an increased risk of CV events. Data from an observational study of 367 general practices in the UK between 2000 and 2004 has suggested that the use of diclofenac and ibuprofen is associated with an increased risk of myocardial infarction (MI) (Hippisley-Cox & Coupland 2005).

Selective COX-2 inhibitors

The COX-2 inhibitors are a new generation of NSAIDs. These drugs were developed to selectively inhibit the COX-2 enzyme with the aim of stopping the production of inflammatory prostaglandins without inhibiting the production of prostaglandins that protect the stomach and intestine. Therefore, these selective COX-2 inhibitors were proposed to provide comparable efficacy to that of nonselective NSAIDs, but with a lower incidence of GI adverse effects. Several COX-2 inhibitors have been developed for the treatment of OA including etodolac and meloxicam which are relatively COX-2 selective, and rofecoxib, celecoxib, valdecoxib, etoricoxib, and lumiracoxib which are highly COX-2 selective.

A review of the efficacy and safety of the COX-2 inhibitors is beyond the scope of this article. Therefore, only the major issues (i.e. their GI effects and potential CV risk) currently surrounding the COX-2 inhibitors will be summarized.

GI effects

There is conflicting data regarding the GI benefit of COX-2 inhibitors compared with the nonselective NSAIDs. Large-scale GI safety studies with rofecoxib [Vioxx Gastrointestinal Outcomes Research (VIGOR) trial] and celecoxib [Celecoxib Long-term Arthritis Safety Study (CLASS)] have demonstrated that these COX-2 inhibitors reduce the incidence of GI adverse events compared with nonselective NSAIDs (Bombardier et al. 2000; Silverstein et al. 2000). However, unpublished data from the CLASS trial have shown that the GI advantage seen with celecoxib at 6 months was not evident after 13 months (FDA 2001). In addition, a review of data from an observational study of 367 general practices in the UK suggested that rofecoxib did not offer a GI benefit over the nonselective NSAIDs (Hippisley-Cox et al. 2005).

CV profile

COX-2 inhibitors appear to suppress the production of prostacyclin, a vasodilator that inhibits platelet aggregation and thereby reduces blood clotting. It has been hypothesized that selective inhibition of COX-2 may alter the balance between the antithrombotic prostacyclin and prothrombotic TXA₂, selectively inhibiting the production of prostacyclin and allowing the effects of thromboxane to predominate, thereby promoting a prothrombotic state (Jones 2005).

Emerging data have raised concerns over an increased risk of CV events with COX-2 inhibitors. Data from the cancer prevention trial Adenomatous Polyp Prevention on Vioxx (APPROVe) suggested that patients receiving rofecoxib had a statistically significant increase in heart attacks and other adverse CV events such as strokes (Bresalier et al. 2005). It is not evident whether the increased risk of CV events seen with rofecoxib is a class effect. However, the Adenoma Prevention with Celecoxib (APC) trial also demonstrated 2.5 times the rate of a major CV event among patients taking celecoxib compared with placebo (Solomon et al. 2005), and there is some evidence for increased CV risk with another COX-2 inhibitor, etoricoxib (Aldington et al. 2005). A systematic review of the clinical literature (from 1996 to March 2005) attempted to determine the relative thromboembolic risks of COX-2 inhibitors and concluded that each COX-2 inhibitor has a unique CV risk profile (Jones 2005). The author noted that the risk of a CV event may depend upon the agent chosen and its COX-2-specific isoform-binding affinity, the CV risk profile of the patient, and the dose and duration of the drug use.

Renal function

In addition to the role of COX-1, COX-2 is also involved in the synthesis of prostaglandins which play a role in modulating renal function. Consequently COX-2 inhibitors have been associated with similar renal adverse effects to those seen with nonselective NSAIDs. Therefore, the COX-2 inhibitors may not offer a clinical advantage over nonselective NSAIDs with regards to avoiding or exacerbating edema, hypertension, and congestive heart failure.

The COX-2 inhibitors rofecoxib and celecoxib have been associated with slightly higher BP compared with nonselective NSAIDs (Whelton et al. 2001; Whelton et al. 2002; Aw et al. 2005). A retrospective cohort study demonstrated that more elderly patients with a previous episode of congestive heart failure prescribed celecoxib survived or remained free of recurrent congestive heart failure than those prescribed either rofecoxib or nonselective NSAIDs. These data suggest that differences may exist between the classes of nonselective NSAIDs and COX-2 inhibitors, and between COX-2 inhibitors (Hudson et al. 2005).

Current treatment guidelines

It is recommended that all pharmacologic agents should be considered in addition to nonpharmacologic measures for the treatment of OA. The first drug of choice for the treatment of inflammation and pain in patients with OA is acetaminophen, which when using the appropriate dosage may be taken safely over the long term, and is inexpensive compared with prescription NSAIDs (ACR 2000; Pendleton et al. 2000; NICE 2001). Alternatively, US guidelines for the medical management of OA of the hip and knee suggest that NSAIDs or joint aspiration in combination with intraarticular injection of glucocorticoids may be considered as first-line pharmacologic therapy in patients with moderate to severe pain, and with signs of joint inflammation (ACR 2000). In patients with risk factors for serious upper GI events and renal toxicity, US guidelines recommend the use of COX-2 selective inhibitors, or nonselective NSAIDs in combination with a gastroprotective agent (misoprostol or a PPI) (ACR 2000).

European (EULAR) evidence-based guidelines for the management of knee OA state that there is good evidence [from at least one randomized, controlled trial (RCT)] to suggest that NSAIDs are more efficacious in providing pain relief than acetaminophen (Pendleton et al. 2000). In patients who fail to achieve adequate symptomatic relief with acetaminophen, European guidelines recommend the use of oral or topical NSAIDs (Pendleton et al. 2000).

Current NICE guidelines on the use of COX-2 inhibitors (celecoxib, rofecoxib, meloxicam, and etodolac) do not recommend the routine use of COX-2 selective inhibitors in patients with OA (NICE 2001). These guidelines state that they should only be used instead of nonselective NSAIDs in patients at high-risk of developing serious GI adverse effects (patients aged ≥ 65 years, using concomitant medication that increases the likelihood of upper GI adverse events, serious comorbidity present, or requiring prolonged use of maximum recommended doses of NSAIDs). It is assumed that these recommendations are based upon the improved cost effectiveness reported with COX-2 inhibitors in this high-risk population, compared with nonselective NSAIDs.

Since the publication of these guidelines, rofecoxib and valdecoxib have been withdrawn from all markets (Table 2). A joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee reviewed the safety of all COX-2 inhibitors (FDA 2005a). They concluded that the risk versus benefit of COX-2 inhibitors favored their continued use in the US and that although all NSAIDs impose similar CV risks, some agents

(naproxen and celecoxib) appeared to be safer than others (e.g. rofecoxib, valdecoxib, diclofenac, and ibuprofen). They also concluded that the CV risks of COX-2 inhibitors may be greater with higher doses, longer durations of therapy, and when used in high-risk individuals. Therefore, they suggested that the use of COX-2 inhibitors and other NSAIDs thought to increase CV risk should be avoided in high-risk individuals. As a result of this meeting, the Food and Drug Administration (FDA) has issued a Public Health Advisory on CV risks from all nonaspirin NSAIDs and recommended the addition of "black box" label warnings for CV risks and GI bleeding for all prescription nonaspirin NSAIDs (FDA 2005b). Similar contraindications and precautions have been recommended by the European Medicines Agency (EMA 2005a) (Table 2).

Table 2 | Current status (October 2007) of COX-2 inhibitors for the treatment of OA

Drug	Current status
Lumiracoxib (Prexige, Novartis)	Approved in EU, Argentina, Brazil, Mexico, South Africa; withdrawn in Australia, Canada
Celecoxib (Celebrex, Pfizer)	Only marketed COX-2 inhibitor in the US Restricted use in EU ^a
Etoricoxib (Arcoxia, Merck)	Not available in US
Valdecoxib (Bextra, Pfizer)	Withdrawn from US (April 2005), suspended in EU
Rofecoxib (Vioxx, Merck)	Withdrawn from all markets following results from the APPROVe trial (September 2004)

^aThe use of COX-2 inhibitors has been restricted in the EU with several contraindications and precautions (EMA 2005a), as follows: COX-2 inhibitors must not be used in patients with established ischemic heart disease and/or cerebrovascular disease (stroke) and in patients with peripheral arterial disease. Healthcare professionals (HCPs) to exercise caution in prescribing COX-2 inhibitors to patients with risk factors for heart disease, such as hypertension, hyperlipidemia, diabetes, and smoking. Advised to use lowest effective dose for shortest possible duration of treatment. Warnings to HCPs and patients that hypersensitivity reactions and rare, but serious and sometimes fatal, skin reactions can occur with all COX-2 inhibitors. In the majority of cases these occur in the first month of treatment and patients with a history of drug allergies may be at greater risk. APPROVe, Adenomatous Polyp Prevention on Vioxx; COX-2, cyclooxygenase-2.

Unmet needs

The pain and joint stiffness associated with OA has debilitating effects on patients, seriously affecting their quality of life. Therefore, patients require a drug which effectively reduces pain and stiffness, and is safe and well tolerated in the long term.

Current treatment options for OA are limited. Nonselective NSAIDs can cause GI adverse events, and are often used in combination with gastroprotective agents. This increases the medication burden, and may lead to cost issues. A large proportion of patients with OA are ≥ 65 years of age, and are likely to be receiving multiple medications for concomitant conditions. Therefore, this medication burden may also lead to compliance issues.

The COX-2 inhibitors provided an alternative treatment to nonselective NSAIDs, particularly for patients at high risk of GI events. However, the withdrawal of rofecoxib and valdecoxib, because of concerns over CV safety and the potential for a rare but

serious skin reaction with valdecoxib, has limited the treatment options available for patients with OA as indicated in Table 2. Celecoxib is the only COX-2 inhibitor available in the US, and the potential risk of CV events has restricted its use in patients with CV disease.

Many patients with OA are elderly with comorbidities such as CV disease. Therefore, there is a need for an agent which is as effective as an NSAID, has a low incidence of GI events, is more cost effective than nonselective NSAIDs in combination with gastroprotective agents, and has a good safety profile.

Clinical evidence with lumiracoxib in OA

Lumiracoxib is a selective COX-2 inhibitor and, unlike the other COX-2 inhibitors (sulfonamides or sulfone derivatives), it is an arylacetic acid derivative (Rordorf et al. 2005). Therefore, it is unlikely to cause an allergic reaction in patients with a hypersensitivity to sulfonamides.

Most data in the form of patient-oriented evidence have been gained from large, randomized, controlled clinical studies with lumiracoxib in patients with OA. Improved quality of life, provided by pain relief and improvements in joint stiffness, is an important outcome in patients with OA. The physical functioning of patients with lumiracoxib has been measured in the majority of studies by the Western Ontario and McMaster Universities OA Index (WOMAC) questionnaire for patients with OA of the knee or hip and by the Australian/Canadian OA Hand Index (AUSCAN) for patients with OA of the hand. Two studies have also utilized the Short Form (SF) 36 Health Survey to assess health-related quality of life, and one pooled analysis employs a scale called the Patient Acceptable Symptom State (PASS).

Pain intensity

Strong level 1 evidence from a systematic review of nine RCTs (Berenbaum et al. 2005), level 2 evidence from three RCTs

Table 3 | Level 1 evidence (taken from a systematic review of nine efficacy studies) of the effect of lumiracoxib on pain intensity in patients with OA of the knee (Berenbaum et al. 2005)

Design	Treatment (no. patients)	PID (100 mm VAS); baseline to mean of 3- and 5-hour pain assessments after dosing on day 0
1-wk, parallel-group RCT	400 mg LX od (144)	19.8
	200 mg CX bid (145)	16.8
	PL (75)	13.4
1-wk, parallel-group RCT ^a	200 mg LX od (105)	19.6
	400 mg LX od (99)	17.8
	200 mg CX bid (101)	17.8
	PL (103)	15.4

^aAlso published in abstract form (Wittenberg et al. 2003).
bid, twice daily; CX, celecoxib; LX, lumiracoxib; OA, osteoarthritis; od, once daily; PID, pain intensity difference; PL, placebo; RCT, randomized controlled trial; VAS, visual analog scale; wk, week.

Table 4 | Effect of lumiracoxib on pain intensity and patient's/physician's global assessment of disease activity in patients with OA of the knee, hip or hand (all published level 2 evidence is cited as original source; level 2 evidence only published within the systematic review of Berenbaum et al. 2005 is cited as such)

Reference	Design and population	Treatment (no. patients)	Outcome [mean change from baseline to end of study (100 mm VAS)]		
			Pain intensity in target knee (mm)	Patient's global assessment of disease activity (mm)	Physician's global assessment of disease activity (mm)
4-week studies					
Berenbaum et al. 2005 ^a	Hip or knee OA db, RCT	100 mg LX od (122) PL (122)	-24.6 -16.8	LX-PL difference in LSM -8.8; <i>P</i> =0.001	NR
Schnitzer et al. 2004a	Hip or knee OA Phase II dose-finding study db, RCT	50 mg LX bid (98) 100 mg LX bid (96) 200 mg LX bid (99) 400 mg LX od (99) 75 mg diclofenac bid (94) PL (97)	Mean overall scores at baseline of 64.7-67.0 were reduced to 33.7-38.4 mm with all doses of LX and diclofenac, and from 67.9 to 50.2 with placebo	-24.3 -24.2 -26.5 -28.1 -27.8 -12.5	-21.8 -23.2 -27.0 -26.5 -23.8 -13.1
Grifka et al. 2004	Hand OA db, mc, RCT	200 mg LX od (205) 400 mg LX od (193) PL (196)	-28.0 -30.0 -19.3	-16.3 -20.9 -9.4	-17.8 -18.7 -12.5
13-week studies					
Lehmann et al. 2005	Knee OA db, dd, mc, RCT	100 mg LX od (420) 100 mg LX od + 200 mg loading dose LX od for first 2 wk (420) 200 mg CX od (420) PL (424)	-26.8 -26.2 -26.6 -21.4	-25.1 -21.9 -22.9 -18.9	-26.3 -25.0 -25.4 -20.4
Sheldon et al. 2005	Knee OA db, dd, mc, RCT	100 mg LX od (391) 100 mg LX od + 200 mg loading dose LX od for first 2 wk (385) 200 mg CX od (393) PL (382)	-25.1 -25.9 -24.1 -18.1	-23.2 -24.6 -19.5 -13.4	-25.5 -26.9 -22.2 -15.7
Tannenbaum et al. 2004	Knee OA db, dd, mc, RCT	200 mg LX od (487) 400 mg LX od (491) 200 mg CX od (481) PL (243)	-26.0 -27.4 -25.2 -19.8	-23.2 -24.1 -22.4 -15.7	-23.0 -23.6 -22.4 -18.0
Fleischmann et al. 2005	Knee OA db, dd, mc, RCT	200 mg LX od (462) 400 mg LX od (463) 200 mg CX od (444) PL (231)	-28.7 -29.7 -27.4 -21.3	-25.3 -25.8 -24.5 -16.1	-27.2 -26.7 -24.5 -18.3
Berenbaum et al. 2005	Hip OA RCT	400 mg LX od (205) 25 mg RX od (102) PL (204)	-21.8 -25.0 -15.1	-18.3 -21.8 -11.6	NR NR NR
52-week studies					
Berenbaum et al. 2005 ^b	Knee OA 39-wk extension of Tannenbaum et al. 2004	200 mg LX od (352) 400 mg LX od (358) 200 mg CX od (348) 200 mg LX od (56) ^c 400 mg LX od (59) ^c 200 mg CX od (56) ^c	-28.1 -28.7 -28.3 -3.3 -5.6 -4.3	-25.2 -24.6 -26.1 -5.2 -5.8 -9.2	NR NR NR NR NR NR
Pavelka et al. 2005 (abstract)	Knee OA 39-wk extension of Lehmann et al. 2005	100 mg LX od (659) 200 mg CX od (327) 100 mg LX od (176) ^d 200 mg CX od (130) ^d	LSM for LX and CX were similar at study end: 33.2 mm and 31.0 mm, respectively	LSM for LX and CX were similar at study end: 36.6 mm and 34.2 mm, respectively	NR
Schnitzer et al. 2004b, Grifka et al. 2005 (abstract)	Hip, knee, or hand OA	400 mg LX od (9117) 500 mg naproxen bid (4730) 800 mg ibuprofen tid (4397)	Reduction in pain intensity with LX was similar to that of NSAIDs [62.7% vs 61.9% (NSAID combined data); <i>P</i> =0.107], regardless of the joint affected ^e	Proportion of patients with improvement in the patient's global assessment of disease activity: 60.3% LX vs 59.1% (ibuprofen and naproxen; <i>P</i> =0.015) ^e	Proportion of patients with improvement in the physician's global assessment of disease activity: 59.2% LX vs 58.3% (ibuprofen and naproxen; <i>P</i> =0.023)

^aAlso published in abstract form (Benevolenskaya et al. 2003); ^bAlso published in abstract form (Schell et al. 2003); ^c171 patients receiving placebo during the core 13-week study were re-randomized to active treatment during extension period; ^d306 patients receiving placebo during the core 13-week study were re-randomized to active treatment during extension period; ^eAll data scored using the 5-point Likert scale. bid, twice daily; CX, celecoxib; db, double-blind; dd, double-dummy; LSM, least squares mean; LX, lumiracoxib; mc, multicenter; NSAID, nonsteroidal antiinflammatory drug; NR, not reported; OA, osteoarthritis; od, once daily; PL, placebo; RCT, randomized controlled trial; RX, rofecoxib; tid, three times daily; VAS, visual analog scale; wk, week.

Table 5 | Effect of lumiracoxib on WOMAC/AUSCAN scores in patients with OA of the knee, hip, or hand (all published level 2 evidence is cited as original source; level 2 evidence only published within the systematic review of Berenbaum et al. 2005 is cited as such)

Reference	Design and population	Treatment (no. patients)	Outcome (mean change from baseline to end of study) WOMAC scores (AUSCAN for OA of hand)			
			Total score	Pain subscale	DPDA subscale	Stiffness subscale
4-week studies						
Berenbaum et al. 2005 ^a	Hip or knee OA db, RCT	100 mg LX od (122) PL (122)	LX-PL difference in LSM -4.5; <i>P</i> =0.021	NR	NR	NR
Schnitzer et al. 2004a	Hip or knee OA Phase II dose- finding study db, RCT	50 mg LX bid (98)	NR	-3.4	-10.3	-1.7
		100 mg LX bid (96)	NR	-2.8	-7.9	-1.3
		200 mg LX bid (99)	NR	-3.2	-10.7	-1.5
		400 mg LX od (99)	NR	-3.8	-13.0	-1.6
		75 mg diclofenac bid (94) PL (97)	NR	-3.3 -1.5	-11.1 -5.4	-1.3 -0.7
Grifka et al. 2004	Hand OA db, mc, RCT	200 mg LX od (205)	-7.7	-3.0	-4.3	-0.6
		400 mg LX od (193)	-10.5	-3.9	-6.0	-0.7
		PL (196)	-5.6	-2.1	-3.1	-0.4
13-week studies						
Lehmann et al. 2005	Knee OA db, dd, mc, RCT	100 mg LX od (420)	-15.2	-3.4	-10.5	-1.3
		100 mg LX od + 200 mg loading dose LX od for first 2 wk (420)	-14.8	-3.2	-10.4	-1.1
		200 mg CX od (420)	-14.7	-3.4	-10.3	-1.1
		PL (424)	-11.3	-2.5	-8.0	-0.9
Sheldon et al. 2005	Knee OA db, dd, mc, RCT	100 mg LX od (391)	-16.9	-3.6	-11.9	-1.5
		100 mg LX od + 200 mg loading dose LX od for first 2 wk (385)	-17.2	-3.7	-12.0	-1.5
		200 mg CX od (393)	-15.6	-3.4	-10.8	-1.4
		PL (382)	-9.5	-2.3	-6.3	-0.9
Tannenbaum et al. 2004	Knee OA db, dd, mc, RCT	200 mg LX od (487)	-14.1	-3.2	-9.8	-1.2
		400 mg LX od (491)	-14.1	-3.2	-9.7	-1.2
		200 mg CX od (481)	-13.4	-3.1	-9.2	-1.2
		PL (243)	-9.4	-2.4	-6.2	-0.9
Fleischmann et al. 2005	Knee OA db, dd, mc, RCT	200 mg LX od (462)	-17.8	-3.7	-12.5	-1.6
		400 mg LX od (463)	-16.9	-3.7	-11.7	-1.4
		200 mg CX od (444)	-16.0	-3.5	-11.0	-1.4
		PL (231)	-9.3	-2.3	-6.1	-0.9
Berenbaum et al. 2005	Hip OA RCT	400 mg LX od (205)	-11.4	-2.7	NR	NR
		25 mg RX od (102)	-14.6	-3.1	NR	NR
		PL (204)	-8.6	-2.1	NR	NR
52-week studies						
Berenbaum et al. 2005 ^b	Knee OA 39-wk extension of Tannenbaum et al. 2004	200 mg LX od (352)	-16.1	-3.6	NR	NR
		400 mg LX od (358)	-16.4	-3.7	NR	NR
		200 mg CX od (348)	-15.5	-3.4	NR	NR
		200 mg LX od (56) ^c	-3.5	-0.4	NR	NR
		400 mg LX od (59) ^c	-2.1	-0.5	NR	NR
Pavelka et al. 2005 (abstract)	Knee OA 39-wk extension of Lehmann et al. 2005	200 mg CX od (327)	LSM for LX and CX were similar at study end: 33.0 mm and 30.7 mm, respectively	NR	NR	NR
		100 mg LX od (176) ^d				
		200 mg CX od (130) ^d				

^aAlso published in abstract form (Benevolenskaya et al. 2003).^bAlso published in abstract form (Schell et al. 2003).^c171 patients receiving placebo during the core 13-week study were re-randomized to active treatment during the extension period.^d306 patients receiving placebo during the core 13-week study were re-randomized to active treatment during the extension period.

AUSCAN, Australian/Canadian OA Hand Index; bid, twice daily; CX, celecoxib; db, double-blind; dd, double-dummy; DPDA, difficulty in performing daily activities; LSM, least squares mean; LX, lumiracoxib; mc, multicenter; NR, not reported; OA, osteoarthritis; od, once daily; PL, placebo; RCT, randomized controlled trial; RX, rofecoxib; wk, week; WOMAC, Western Ontario and McMaster Universities OA Index.

published in full, including the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET) (Schnitzer et al. 2004b; Lehmann et al. 2005; Sheldon et al. 2005), one RCT published in abstract form (Pavelka et al. 2005), and an additional analysis from TARGET published in abstract form (Grifka et al. 2005), has shown that the pain relief [as assessed by pain intensity on a visual analog scale (VAS)] with lumiracoxib is superior to that gained with placebo and similar to that with celecoxib, rofecoxib, ibuprofen, naproxen, and diclofenac in patients with OA of the hand, hip, or knee (Tables 3 and 4). The efficacy of lumiracoxib does not appear to be dose dependent, with the 100 mg dose providing similar efficacy to the 400 mg dose.

Level 1 and level 2 evidence from these studies also shows that lumiracoxib improves patients' and physicians' assessment of disease activity, as determined by a questionnaire (Table 4). The reduction in scores with lumiracoxib were superior to placebo and comparable with celecoxib, rofecoxib, ibuprofen, naproxen, and diclofenac. These findings suggest that lumiracoxib is effective in managing pain relief in patients with OA, and has comparable efficacy to other available NSAIDs.

Pain intensity was reduced by lumiracoxib 400 mg/day (four times greater than the recommended dosage for OA) to a significantly greater extent than placebo and to a comparable degree as celecoxib 200 mg/day (twice the recommended OA dosage) 3 and 5 hours postdose in patients with knee OA (Wittenberg et al. 2006).

Joint stiffness and function

Level 1 (Berenbaum et al. 2005) and level 2 evidence (Lehmann et al. 2005; Sheldon et al. 2005) demonstrated that lumiracoxib improves joint stiffness and overall function [assessed using the difficulty in performing daily activities (DPDA) and stiffness subscales of the WOMAC questionnaire or the AUSCAN] compared with placebo (Table 5). These improvements were similar

to that achieved with diclofenac and celecoxib, and are expected to have a positive impact on the quality of life of the patient.

SF-36 Health Survey

The SF-36 Health Survey is a validated questionnaire which provides a measure of generic health by eight health profiles including physical functioning and mental health (Ware 1993). SF-36 was used in two RCTs to determine health-related quality of life in patients with OA receiving lumiracoxib (Fleischmann et al. 2005; Sheldon et al. 2005). The results showed that lumiracoxib and celecoxib were statistically superior to placebo in the SF-36 physical component (data not reported; defined as limitations in physical activity because of health problems) (Fleischmann et al. 2005; Sheldon et al. 2005) and mental health component (defined as psychologic distress and wellbeing) (Sheldon et al. 2005) at week 13.

Responders

Analyses of response to lumiracoxib treatment were also performed using the Outcome Measures in Clinical Trials-Osteoarthritis Research Society International (OMERACT-OARSI) criteria (Dougados et al. 2000; Pham et al. 2003). Responders to treatment were defined as patients who either had: a) reduction of $\geq 50\%$ from baseline and an absolute reduction of ≥ 20 either in OA pain intensity (100 mm VAS) or WOMAC DPDA subscale score (rescaled to 0–100); or b) reduction of $\geq 20\%$ and an absolute reduction of ≥ 10 in at least two of the following variables: OA pain intensity (100 mm VAS), WOMAC DPDA subscale score (rescaled to 0–100) or patient's global assessment of disease activity (100 mm VAS). These criteria demonstrated that a significantly greater proportion of patients receiving active treatment were considered responders compared with placebo (data not stated, reported graphically; all $P < 0.05$ vs placebo) (Berenbaum et al. 2005; Fleischmann et al. 2005; Lehmann et al. 2005; Sheldon et al. 2005).

Table 6 | Patient satisfaction (%) with lumiracoxib 100 mg/day versus celecoxib 200 mg/day according to Patient Acceptable Symptom State (PASS). Pooled analysis of Lehmann et al. (2005) and Sheldon et al. (2005) (from Dougados et al. 2007)

	Lumiracoxib 100 mg/day (n=811)	Lumiracoxib 100 mg/day with initial dose of 200 mg/day (n=805)	Celecoxib 200 mg/day (n=813)	Placebo (n=806)
Pain intensity				
Week 2	30.9 ^a	33.5 ^a	29.8 ^a	17
Week 13	43.3 ^a	45.3 ^a	42.2 ^b	35.5
Disease activity				
Week 2	29.6 ^a	31.7 ^a	28.8 ^a	17.4
Week 13	42.8 ^a	43.9 ^a	39.5 ^a	31.6
WOMAC function score				
Week 2	32.3 ^a	33.7 ^a	31.9 ^a	19.1
Week 13	41.6 ^a	41.4 ^a	38.7 ^a	29.5

^a $P < 0.001$ vs placebo.
^b $P < 0.01$ vs placebo.
 WOMAC, Western Ontario and McMaster Universities OA Index.

A pooled analysis of the trials by Lehmann et al. (2005) and Sheldon et al. (2005) investigated the response to treatment using PASS (Dougados et al. 2007). PASS defines the symptom score beyond which patients consider themselves to be well (0–100 mm VAS): ≤ 32.3 mm for pain intensity, ≤ 32 mm for disease activity, and ≤ 21.08 for WOMAC function score. A significantly greater proportion of patients receiving lumiracoxib 100 mg/day, with and without an initial dose of 200 mg/day, were satisfied after 2 and 13 weeks compared with placebo; there was no significant difference between lumiracoxib and celecoxib 200 mg/day (Table 6). The response rate, measured by Minimally Clinical Important Improvement (MCII) in a patient's symptom score, was similar for lumiracoxib and celecoxib, and significantly greater than with placebo (Dougados et al. 2007).

General tolerability

The most common adverse events with lumiracoxib in clinical trials typically included headache and nasopharyngitis. As expected, GI effects were also present, with nausea, diarrhea, dyspepsia, and upper abdominal pain being the most frequent minor GI-related adverse events. The incidence of these adverse events was similar to that with celecoxib, diclofenac, ibuprofen, and naproxen. TARGET is the only long-term study assessing the safety of lumiracoxib over 52 weeks in a large population of patients (9117 receiving lumiracoxib treatment). Table 7 provides details of the adverse events experienced with lumiracoxib in this study. Discontinuation due to adverse events was similar between active treatment groups and placebo, although there were a greater number of discontinuations with diclofenac than lumiracoxib (14% vs 3–5%) in one RCT (Schnitzer et al. 2004a). In addition, Schnitzer et al. (2004a) reported that there was no dosage-related trend with lumiracoxib in the incidence of these adverse events.

GI safety

Evidence suggests that lumiracoxib is associated with a comparable incidence of GI complications to other COX-2 inhibitors, and a lower risk of upper GI ulcer complications compared with ibuprofen or naproxen in patients not taking aspirin.

Level 1 evidence from a pooled analysis of 15 phase II and phase III RCTs in patients with OA or RA, demonstrated that treatment with lumiracoxib (100–1200 mg; 5439 patients) was associated with a significantly lower rate of perforations, obstructions, symptomatic ulcers, and bleedings than the nonselective NSAIDs (1.7 versus 13.7 events per 100 patient-years for lumiracoxib 200–400 mg) (Hawkey et al. 2006) (Table 8). The incidence was similar to that for celecoxib and rofecoxib (1.4 events per 100 patient-years).

Level 2 evidence from two RCTs of short duration (8 days) in healthy volunteers showed that lumiracoxib (200 or 800 mg) is associated with a lower incidence of gastric and duodenal erosion, compared with the nonselective NSAID naproxen (Rordorf et al. 2003; Atherton et al. 2004; Table 8). In addition, results from a study of 13 weeks' duration in patients with OA demonstrated that lumiracoxib 200 or 400 mg was associated with a significant lower incidence of gastroduodenal ulcers (≥ 3 mm and ≥ 5 mm) compared with the nonselective NSAID ibuprofen ($P < 0.001$ and $P < 0.005$, respectively), a similar incidence to that achieved with celecoxib (Hawkey et al. 2004a).

Gastric erosion is a surrogate marker for the development of peptic ulceration or other major GI adverse effects. Therefore, the TARGET outcomes study in 18 325 patients with OA was conducted to determine the clinical relevance of these

Table 7 | Level 2 evidence for the most common adverse events and discontinuations due to adverse events with lumiracoxib in patients with hip, knee or, hand OA (Schnitzer et al. 2004b)

Outcome	Lumiracoxib vs ibuprofen substudy		Lumiracoxib vs naproxen substudy	
	Lumiracoxib (n=4376)	Ibuprofen (n=4397)	Lumiracoxib (n=4741)	Naproxen (n=4730)
Total number of patients with AEs	3586 (82%)	3559 (81%)	3647 (77%)	3717 (79%)
Total number of patients with SAEs	297 (7%)	272 (6%)	291 (6%)	294 (6%)
Prespecified GI events	1855 (42%)	1851 (42%)	1785 (38%)	1988 (42%)
dyspepsia	1230 (28%)	1205 (27%)	1037 (22%)	1119 (24%)
abdominal pain upper	380 (9%)	452 (10%)	535 (11%)	695 (15%)
diarrhea	285 (7%)	247 (6%)	273 (6%)	195 (4%)
nausea	244 (6%)	261 (6%)	221 (5%)	264 (6%)
abdominal pain	147 (3%)	153 (4%)	181 (4%)	187 (4%)
Discontinuations due to AEs (including SAEs)	718 (16%)	802 (18%)	723 (15%)	855 (18%)

AE, adverse event; GI, gastrointestinal; OA, osteoarthritis; SAE, serious adverse event.

Table 8 | Evidence for the incidence of GI erosions and ulcers with lumiracoxib

Reference	Design and population	Treatment (no.)	Incidence of GI erosions and ulcers
Level 1 evidence			
Hawkey et al. 2006	Pooled analysis (15 phase II and III RCTs) Pts with hip, knee, hand, or spine OA, or symptomatic RA pts 1–52 wk, db, RCT	100–1200 mg LX od 200/400 mg CX od 25 mg RX od 75 mg diclofenac bid 800 mg ibuprofen tid 500 mg naproxen bid PL	Incidence of PUBs: 1.7 events per 100 patient-years, LX 200/400 mg; 1.4 events per 100 patient-years, celecoxib and rofecoxib; 13.7 events per 100 patient-years, nonselective NSAIDs Frequency of symptomatic ulcers: 0.4% LX 200/400 mg, 0.4% CX and RX, 2.5% nonselective NSAIDs
Endoscopic studies: level 2 evidence			
Atherton et al. 2004	Healthy volunteers 8 d, db, dd, RCT (3-way crossover; 18-d washout period)	800 mg LX od (24) PL (24) 500 mg naproxen bid (24)	No subjects receiving LX developed gastroduodenal erosions 3 subjects (12.5%) on PL developed gastroduodenal erosions (1–6 erosions per individual) 18 subjects (75%) on naproxen had a total of 255 gastroduodenal erosions (1–32 erosions per individual). Erosions were predominantly in the gastric antrum
Rordorf et al. 2003	Healthy male volunteers 8 d, db, dd, RCT	200 mg LX bid (20) PL (20) 500 mg naproxen bid (20)	No duodenal erosions (endoscopy grade 3 or above) with LX or PL 13/20 (65%) pts had duodenal erosions with naproxen No gastric erosions with LX One subject in naproxen group developed an asymptomatic gastric ulcer One subject in PL group developed a grade 4 gastric erosion (6–10 erosions)
Hawkey et al. 2004a	Pts with hip, knee, or hand OA 13 wk, db, dd, mc, RCT	200 mg LX od (257) ^a 400 mg LX od (253) ^a 800 mg ibuprofen tid (248) ^a 200 mg CX od (253) ^a	The cumulative incidence of gastroduodenal ulcers (≥3 mm diameter) was 4.3% and 4.0% for 200 mg LX and 400 mg LX, respectively (both $P<0.001$ vs ibuprofen), 15.7% for ibuprofen and 3.2% for CX The cumulative incidence of gastroduodenal ulcers (≥5 mm diameter) was 3.9% and 3.6% for 200 mg LX and 400 mg LX, respectively (both $P<0.005$ vs ibuprofen), 12.5% for ibuprofen and 2.8% for CX The number of pts with >10 gastroduodenal erosions was significantly greater with ibuprofen (6%) compared with 200 mg LX (1.2%; $P<0.01$), 400 mg LX (1.6%, $P<0.05$), and CX (2.4%, $P<0.05$) 72.4% and 76.7% of pts receiving 200 mg LX and 400 mg LX, respectively had no visible injury of gastric mucosa compared with 55.2% of pts receiving ibuprofen (both $P<0.001$ vs ibuprofen) and 75.5% of pts receiving CX 83.7% and 87.4% of pts receiving 200 mg LX and 400 mg LX, respectively, had no visible injury of gastric mucosa compared with 74.2% of pts receiving ibuprofen ($P<0.05$ LX 200 mg, $P<0.001$ LX 400 mg vs ibuprofen) and 87.7% of pts receiving CX Lower level mucosal injury: only one pt developed an esophageal ulcer (LX 400 mg)
Outcome study: level 2 evidence			
Schnitzer et al. 2004b	Pts with hip, knee, hand, or spine OA 52 wk, db, dd, mc, RCT	400 mg LX od (4376) 800 mg ibuprofen tid (4397) 400 mg LX od (4741) 500 mg naproxen bid (4730)	Number (incidence) of upper GI ulcer complications ^b : 10 (0.23%) LX vs 33 (0.75%) ibuprofen (HR 0.29; $P=0.0006$); 19 (0.40%) LX vs 50 (1.06%) naproxen (HR 0.37; $P=0.0002$). The majority of these GI complications were presented as melena or hematochezia Number (incidence) of upper GI ulcer complications in nonaspirin population ^b : 5/3401 (0.15%) LX vs 28/3431 (0.82%) ibuprofen (HR 0.17; $P=0.0003$); 9/3549 (0.25%) LX vs 36/3537 (1.02%) naproxen (HR 0.24; $P=0.0001$) Number (incidence) of upper GI ulcer complications in aspirin population ^b : 5/975 (0.51%) LX vs 5/966 (0.52%) ibuprofen (HR 0.92; $P=0.9008$); 10/1192 (0.84%) LX vs 14/1193 (1.17%) naproxen (HR 0.73; $P=0.4502$) Number (incidence) of symptomatic uncomplicated ulcers ^c : 58/9117 (0.64%) LX vs 103/9127 (1.13%) nonselective NSAIDs (HR 0.55; $P=0.0003$)
^a Modified safety population (defined as all patients who underwent at least one postbaseline endoscopy). ^b Definite or probable upper GI ulcer complications (clinically significant bleeding, perforation, or obstruction from erosive or ulcer disease). ^c Ulcers discovered when endoscopy was done for dyspepsia. bid, twice daily; CX, celecoxib; d, day; db, double-blind; dd, double-dummy; GI, gastrointestinal; HR, hazard ratio; LX, lumiracoxib; mc, multicenter; NSAIDs, nonsteroidal antiinflammatory drugs; OA, osteoarthritis; od, once daily; PL, placebo; pts, patients; PUBs, perforations, obstructions, symptomatic ulcers, and bleedings; RA, rheumatoid arthritis; RCT, randomized controlled trial; RX, rofecoxib; RCT; tid, three times daily; wk, week.			

endoscopic findings (Schnitzer et al. 2004b; Hawkey et al. 2004b; Table 8). This study showed that patients receiving lumiracoxib at a dose of 400 mg, which is four-fold greater than the currently indicated dosage of 100 mg for OA, had a significantly lower risk of upper GI ulcer complications than patients receiving ibuprofen or naproxen. In contrast, in patients receiving low-dose aspirin (75–100 mg/day), the incidence of ulcer complications with lumiracoxib was similar to that with ibuprofen and naproxen, and provided no additional GI benefit.

It has been determined that using lumiracoxib rather than ibuprofen or naproxen for 1 year would prevent one severe upper GI event for every 170 patients treated (nonaspirin and aspirin populations combined) (Bannwarth & Berenbaum 2005). In comparison, in the nonaspirin population lumiracoxib would prevent one severe upper GI event for every 139 patients treated.

Cardiovascular safety

Weak level 1 evidence from a meta analysis of 22 RCTs ranging from ≥ 1 week and up to 1 year in duration in patients with either OA or RA found no evidence that lumiracoxib was associated with a significant increase in risk for a CV event compared with naproxen, other NSAIDs (diclofenac, ibuprofen, celecoxib, rofecoxib) or placebo (Matchaba et al. 2005; Table 9). A total of 15 studies were in patients with OA. The incidence of CV events in patients with OA is provided in Table 10.

Table 9 | The risk of CV events with lumiracoxib in patients with OA or RA: results from a meta analysis of all RCTs ≥ 1 week and up to 1 year (Matchaba et al. 2005)

CV event	RR (lumiracoxib vs placebo)	RR (lumiracoxib vs naproxen)	RR (lumiracoxib vs nonnaproxen NSAID)
APTC	1.08 (15/7011 LX; 6/3234 PL)	1.49 (50/5964 LX; 31/5411 naproxen)	0.83 (22/6126 LX; 24/5058 nonnaproxen)
Myocardial event	1.27 (6/7011 LX; 2/3234 PL)	1.69 (22/5964 LX; 12/5411 naproxen)	0.80 (7/6126 LX; 8/5058 nonnaproxen)
Stroke	0.59 (4/7011 LX; 3/3234 PL)	1.42 (20/5964 LX; 13/5411 naproxen)	0.91 (9/6126 LX; 9/5058 nonnaproxen)

APTC, Antiplatelet Trialists' Collaboration composite CV endpoint of myocardial infarction, stroke (ischemic and hemorrhagic), and CV death; CV, cardiovascular; LX, lumiracoxib; NSAID, nonsteroidal antiinflammatory drug; PL, placebo; RCT, randomized controlled trial; RR, relative risk.

The evidence from this meta analysis is weak because the majority of the studies reported were of 4 or 13 weeks' duration. Few CV events were reported with lumiracoxib during this period (Table 10), and it is unlikely that evidence of CV

events would be demonstrated after such a short period of drug exposure. Only TARGET was of adequate duration (1 year) to provide meaningful level 2 evidence for the incidence of CV events with lumiracoxib. However, 1 year may be not sufficient to determine long-term CV risk, and studies of longer duration may be required. Furthermore, a major shortcoming of TARGET was the exclusion of patients with a history of CV disease. Only patients at increased risk of coronary heart disease were eligible provided that they had received low-dose aspirin (75–100 mg daily) for a minimum of 3 months prior to randomization.

Of the 34 668 patients included in this meta analysis, 18 325 were from TARGET. This RCT was divided into two substudies to determine the CV safety of lumiracoxib (400 mg once daily; n=4741) compared with naproxen (500 mg twice daily; n=4730) and lumiracoxib (400 mg once daily; n=4376) compared with ibuprofen (800 mg three times daily; n=4397) (Farkouh et al. 2004).

Approximately 24% (n=4326) of patients participating in TARGET were taking low-dose aspirin, although only 36% (n=1561) of these were classified as high CV risk. The incidence of MI did not differ significantly between lumiracoxib and either ibuprofen or naproxen, irrespective of aspirin use. However, in the naproxen substudy in patients not taking low-dose aspirin fewer patients had MIs in the naproxen 500 mg twice-daily group (four events, 0.11%) compared with the lumiracoxib group (ten events, 0.28%) ($P=0.1454$). The dose of lumiracoxib used in TARGET was four times the current recommended dose of 100 mg for OA, therefore, it may be expected that any CV risk would be reduced at the indicated dose.

In healthy subjects, lumiracoxib does not affect the *ex-vivo* antiplatelet aggregation activity of low-dose aspirin (Jermamy et al. 2005). In contrast, naproxen inhibits platelet aggregation and has been suggested to have an antithrombotic effect, suppressing thromboxane production to a similar level as low-dose aspirin (Capone et al. 2004). This property may explain the reduced incidence of MI with naproxen compared with lumiracoxib, although this remains debatable. Farkouh et al. (2004) highlighted that the absence of a placebo arm in this study made it difficult to ascertain the real risk of MI with lumiracoxib alone.

Level 1 evidence from another meta analysis revealed no significant difference in cerebrovascular event risk in patients taking lumiracoxib compared with placebo, nonselective NSAIDs, or other COX-2 inhibitors. A slightly higher risk was found compared specifically with naproxen (OR 1.09, 95% CI 0.58, 2.04) and ibuprofen (OR 1.31, 95% CI 0.57, 2.98), although this did not reach significance (Chen & Ashcroft 2006). The authors concluded that any increase in CV risk with COX-2 inhibitors must therefore be mainly due to risk of MI.

A further meta analysis that included six lumiracoxib trials revealed no effect on arrhythmia risk, although the authors stated that the results were inconclusive due to the limited number of studies (Zhang et al. 2006).

Table 10 | Incidence and relative risk of CV events with lumiracoxib in patients with OA: results from a meta analysis of RCTs (Matchaba et al. 2005)^a

Reference	Duration of study (wk)	Treatment (dose)	Number of APTC events (safety population)	Number of myocardial events (safety population)	Number of stroke events (safety population)
Berenbaum et al. 2005	1	LX (200/400 mg)	0/204	0/204	0/204
		PL	0/103	0/103	0/103
			RR: no events	RR: no events	RR: no events
Wittenberg et al. 2003	1	LX (400 mg)	1/144	1/144	0/144
		PL	0/75	0/75	0/75
			RR not estimable	RR not estimable	RR: no events
Benevolenskaya et al. 2003	4	LX (100 mg)	0/122	0/122	0/122
		PL	0/122	0/122	0/122
			RR: no events	RR: no events	RR: no events
Grifka et al. 2004	4	LX (200/400 mg)	0/398	0/398	0/398
		PL	0/196	0/196	0/196
			RR: no events	RR: no events	RR: no events
Schnitzer et al. 2004a	4	LX (50/100/200/400 mg)	0/392	0/392	0/392
		PL	0/97	0/97	0/97
		Diclofenac (75 mg)	0/94	0/94	0/94
			RR: no events	RR: no events	RR: no events
Hawkey et al. 2003	6	LX (400 mg) RX (25 mg)	NR	NR	NR
Fleischmann et al. 2005	13	LX (200/400 mg)	2/925	2/925	0/925
		PL	0/231	0/231	0/231
		CX (200 mg)	NR	NR	NR
			RR not estimable	RR not estimable	RR: no events
Tannenbaum et al. 2004	13	LX (200/400 mg)	1/978	1/978	0/978
		PL	0/243	0/243	0/243
Novartis data on file 2002 ^b	13	LX (400 mg)	1/205	0/205	0/205
		PL	2/204	1/204	1/204
		RX (25 mg)	NR	NR	NR
			RR 0.46	RR not estimable	RR not estimable
Hawkey et al. 2004	13	LX (200/400 mg)	1/524	1/524	0/524
		Ibuprofen (800 mg)	1/260	1/260	0/260
		CX (200 mg)	NR	NR	NR
			RR 0.46	RR 0.46	RR: no events
Sheldon et al. 2005	13	LX (100 mg)	1/776	0/776	0/776
		PL	1/382	0/382	1/382
			RR 0.43	RR: no events	RR not estimable
Lehmann et al. 2005	13	LX (100 mg)	2/840	0/840	1/840
		PL2/840	1/424	1/424	0/424
		1/424	RR 0.96	RR not estimable	RR not estimable
Schell et al. 2003 ^c	39	LX (100 mg)	NR	NR	NR
		LX (400 mg)			
		CX (200 mg)			
Pavelka et al. 2005 (abstract)	39	LX (100 mg)	NR	NR	NR
		CX (200 mg)			
Farkouh et al. 2004 ^d	52	LX (400 mg)	40/4741	18/4741	16/4741
		Naproxen (500 mg)	27/4730	10/4730	12/4730
		LX (400 mg)	RR 1.44	RR 1.75	RR 1.30
		Ibuprofen (800 mg)	19/4376	5/4376	8/4376
			23/4397	7/4397	9/4397
			RR 0.79	RR 0.68	RR 0.85

^aThese data are not available in the primary references. Data for the incidence of CV events with the COX-2 comparators (celecoxib or rofecoxib) were not reported, therefore it is not provided in this table.

^bPublished as Berenbaum et al. 2005.

^cExtension of Tannenbaum et al. 2004.

^dTARGET study.

APTC, Antiplatelet Trialists' Collaboration composite CV endpoint of myocardial infarction, stroke (ischemic and hemorrhagic), and CV death; COX-2, cyclooxygenase-2; CV, cardiovascular; CX, celecoxib; LX, lumiracoxib; NR, not reported; OA, osteoarthritis; PL, placebo; RR, relative risk; RCT, randomized controlled trial; RX, rofecoxib; TARGET, Therapeutic Arthritis Research and Gastrointestinal Event Trial; wk, week.

Table 11 | Level 2 evidence for liver function outcomes with lumiracoxib in healthy volunteers and OA patients

Reference	Design and population	Treatment (no.)	Liver function outcomes
Rordorf et al. 2003	Healthy male volunteers 8 d, db, dd, RCT	200 mg LX bid (20) PL (20) 500 mg naproxen bid (20)	ALT/AST elevations (fold increase over ULN ranged from 1.1 to 4.2 for AST and 1.1 to 2.2 for ALT): 4 pts LX, 4 pts PL, 1 pt naproxen
Lehmann et al. 2005	Knee OA 13 wk, db, dd, mc, RCT	100 mg LX od (420) 100 mg LX od + 200 mg loading dose LX od for first 2 wk (420) 200 mg CX od (420) PL (424)	Incidence of liver function parameter elevations >3 x ULN: 0.2% 100 mg LX + loading dose, 0.5% PL, 0.2% CX
Sheldon et al. 2005	Knee OA 13 wk, db, dd, mc, RCT	100 mg LX od (391) 100 mg LX od + 200 mg loading dose LX od for first 2 wk (385) 200 mg CX od (393) PL (382)	Incidence ALT/AST levels >3 x ULN: 0.3% for both LX and CX, 0% PL
Tannenbaum et al. 2004	Knee OA 13 wk, db, dd, mc, RCT	200 mg LX od (487) 400 mg LX od (491) 200 mg CX od (481) PL (243)	Incidence ALT/AST levels >3 x ULN: 2 pts LX 200 mg, 3 pts LX 400 mg, 4 pts CX. None were accompanied by clinical symptoms All cases resolved either while receiving study drug or after treatment had stopped. No clinical symptoms were associated with elevations
Fleischmann et al. 2005	Knee OA 13 wk, db, dd, mc, RCT	200 mg LX od (462) 400 mg LX od (463) 200 mg CX od (444) PL (231)	Incidence ALT >3 x ULN: 0.4% 200 mg LX, 2.6% 400 mg LX, 0.0% CX, 0.4% PL Incidence AST >3 x ULN: 0.2% 200 mg LX, 1.1% 400 mg LX, 0.2% CX, 0.4% PL All cases resolved either while receiving study drug or after treatment had stopped. No clinical symptoms were associated with elevations
Schnitzer et al. 2004b	Hip, knee, hand, or spine OA 52 wk, db, dd, mc, RCT	400 mg LX od (4376) 800 mg ibuprofen tid (4397) 400 mg LX od (4741) 500 mg naproxen bid (4730)	Proportion of pts with ALT/AST concentrations >3 x ULN was greater with LX than with ibuprofen or naproxen [2.57% (n=230) vs 0.63% (n=56) (HR 3.97)] 9 pts had probable or possible drug-induced clinical hepatitis: 6 events (0.07%) LX, 2 events (0.05%) ibuprofen, 1 event (0.02%) naproxen Abnormalities resolved on cessation of treatment. No cases of liver failure, transplantation, or death attributable to drug-induced hepatitis reported

ALT, alanine aminotransferase; AST, aspartate aminotransferase; bid, twice daily; CX, celecoxib; d, day; db, double-blind; dd, double-dummy; GI, gastrointestinal; HR, hazard ratio; LX, lumiracoxib; mc, multicenter; od, once daily; OA, osteoarthritis; PL, placebo; pts, patients; RCT, randomized controlled trial; tid, three times daily; ULN, upper limit of normal; wk, week.

Liver function

Level 2 evidence from six RCTs in healthy volunteers (one study) and patients with OA (five studies) showed that a small proportion of patients receiving a high dose of lumiracoxib (400 mg) experienced clinically relevant elevations in the liver function enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST), which resolved on cessation of treatment (Table 11). These elevations were greater than in patients receiving ibuprofen or naproxen (Schnitzer et al. 2004b). However, at the indicated dose of 100 mg, the incidence was similar to that of celecoxib and placebo.

There is some evidence that higher doses of lumiracoxib may be associated with changes in liver function in some patients. Eleven cases of severe hepatic adverse reactions, including nine cases of liver failure, two deaths, and three liver transplants, at least possibly related to lumiracoxib have been reported among the estimated 7 million patients who have been exposed to the drug since its launch

(MHRA 2007). Most of these reports were associated with doses of 200 to 400 mg/day. Nevertheless, there has been one report of a transient liver reaction among the estimated 5400 patients receiving the drug at 100 mg in the UK (MHRA 2007).

Renal function

The incidence of edema with lumiracoxib in five RCTs in patients with OA is shown in Table 12. Results from these studies showed that the incidence of edema with lumiracoxib did not appear to be dose-related and was infrequent in the majority of studies (ranging from 0% to 5%), with an incidence similar to that with celecoxib, diclofenac, naproxen, and ibuprofen. The incidence was increased in one RCT (11.5% for lumiracoxib 100 mg), but was also high for placebo (4.1%) in this study.

Evidence from TARGET, in which 45% of patients had hypertension, also showed that lumiracoxib 400 mg had a significantly less

Table 12 | Level 2 evidence for the incidence of edema with lumiracoxib treatment in patients with OA

Reference	Design	Treatment (no. patients)	Number (%) of patients with peripheral edema
Grifka et al. 2004	Hand OA 4 wk, db, mc, RCT	200 mg LX od (205)	1 (0.5)
		400 mg LX od (193)	0 (0.0)
		PL (196)	0 (0.0)
Schnitzer et al. 2004a	Hip or knee OA Phase II dose- finding study 4 wk, db, RCT	50 mg LX bid (98)	5 (5.1)
		100 mg LX bid (96)	11 (11.5)
		200 mg LX bid (99)	8 (8.1)
		400 mg LX od (99)	8 (8.1)
		75 mg diclofenac bid (94) PL (97)	5 (5.3) 4 (4.1)
Tannenbaum et al. 2004	Knee OA 13 wk, db, dd, mc RCT	200 mg LX od (487)	6 (1.2)
		400 mg LX od (491)	4 (0.8)
		200 mg CX od (481)	6 (1.2)
		PL (243)	4 (1.6)
Fleischman et al. 2005	Knee OA 13 wk, db, dd, mc RCT	200 mg LX od (462)	11 (2.4)
		400 mg LX od (463)	10 (2.2)
		200 mg CX od (444)	12 (2.7)
		PL (231)	4 (1.7)
Zacher et al. 2005 (abstract)	Hip, knee, hand, or spine OA 52 wk, db, dd, mc, RCT	400 mg LX od (4376)	Incidence in nonaspirin population: LX vs ibuprofen/naproxen (combined data) 4.6% vs 4.7%
		800 mg ibuprofen tid (4397)	
		400 mg LX od (4741)	Incidence in aspirin population: LX vs ibuprofen/naproxen (combined data) 5.0% vs 5.5%
		500 mg naproxen bid (4730)	

bid, twice daily; CX, celecoxib; db, double-blind; dd, double-dummy; LX, lumiracoxib; mc, multicenter; OA, osteoarthritis; od, once daily; PL, placebo; RCT, randomized controlled trial; tid, three times daily; wk, week.

pronounced effect on systolic blood pressure (SBP) and diastolic blood pressure (DBP) compared with the nonselective NSAIDs (mean change from baseline SBP +0.4 mmHg vs +2.1 mmHg; DBP -0.1 mmHg vs +0.5 mmHg; both $P < 0.0001$). Farkouh et al. (2004) suggested that this may be due to reduced sodium retention in patients receiving lumiracoxib.

Additional evidence from TARGET, published in abstract form, showed that the incidence of *de-novo* hypertension with lumiracoxib was low and similar to that with naproxen (Zacher et al. 2005; Table 13). The incidence of *de-novo* hypertension was greater with ibuprofen compared with lumiracoxib. Therefore, it is unlikely that the lower dose of lumiracoxib indicated for OA will increase hypertension. These effects were seen in patients who were also receiving concomitant aspirin.

A subsequent meta analysis that included six lumiracoxib trials in patients with OA or RA indicated no effect of the drug at a median dosage of 300 mg/day on overall renal function (RR 1.07, 95%

Table 13 | The incidence of *de-novo* hypertension with lumiracoxib treatment in patients with OA (level 2 evidence from TARGET; Zacher et al. 2005)

Population	Incidence of <i>de-novo</i> hypertension (%)
Nonaspirin population	
Lumiracoxib vs ibuprofen/naproxen (combined data)	5.0 vs 6.5 ($P < 0.01$)
Lumiracoxib vs ibuprofen	5.0 vs 7.9 ($P < 0.01$)
Lumiracoxib vs naproxen	5.0 vs 5.2
Aspirin population	
Lumiracoxib vs ibuprofen/naproxen (combined data)	5.8 vs 6.5 ($P = 0.593$)
Lumiracoxib vs ibuprofen	5.0 vs 7.2 ($P = 0.267$)
Lumiracoxib vs naproxen	6.4 vs 6.1
OA, osteoarthritis	

CI 0.68, 1.70), including peripheral edema (RR 1.31, 95% CI 0.75, 2.31), hypertension (RR 0.94, 95% CI 0.42, 2.12), or renal dysfunction demonstrated by serum urea, creatinine, kidney disease or renal failure (RR 0.75, 95% CI 0.17, 3.32) (Zhang et al. 2006).

Drug interactions

Lumiracoxib is metabolized by the cytochrome P450 isoform 2C9 (CYP 2C9) (Mangold et al. 2004; Rordorf et al. 2005). However, lumiracoxib has no significant pharmacokinetic interactions with the CYP 2C9 substrate, warfarin (Bonner et al. 2003), or the CYP 2C9 inhibitor, fluconazole (Scott et al. 2004a). Therefore, it is anticipated that lumiracoxib has a low potential for drug–drug interactions with other CYP 2C9 substrates. Coadministration of lumiracoxib with common treatments for dyspepsia (an aluminum hydroxide/magnesium hydroxide antacid or omeprazole) has also been demonstrated to have no clinically significant effect on the single-dose plasma pharmacokinetics of lumiracoxib (Scott et al. 2004b). In addition, moderate hepatic impairment and mild to moderate renal impairment do not appear to influence lumiracoxib exposure (Kalbag et al. 2004; Rordorf et al. 2005).

Economic evidence and resource utilization

There is no published evidence of the cost effectiveness of lumiracoxib.

The acquisition cost of lumiracoxib in the UK is less than that of celecoxib (net price 100 mg x 30 lumiracoxib £17.24 vs £21.55 for celecoxib), and greater than that of nonselective NSAIDs, many of which are in generic form (BNF 2005).

Looking beyond acquisition cost, reducing the incidence (and subsequent management) of clinically significant ulcer complications should have a beneficial effect on overall costs of

managing OA. A cost-effectiveness and cost-utility analysis in patients at average risk of GI and CV events showed that an NSAID in combination with a PPI costs an incremental \$US45 350 per additional ulcer complication avoided and \$US309 666 per quality-adjusted life year (QALY) gained compared with an NSAID alone (Spiegel et al. 2005). A cost-utility analysis for the long-term treatment of OA or RA has suggested that the use of the first-generation COX-2 inhibitors rofecoxib or celecoxib is only cost effective in patients with a previous bleeding ulcer compared with the nonselective NSAID naproxen (Spiegel et al. 2003). Cost comparisons of lumiracoxib with nonselective NSAIDs (with or without gastroprotective agents) in both patients at low and high risk of GI complications are needed to determine whether the degree of risk reduction offsets their increased cost.

Clinical evidence demonstrates that lumiracoxib provided no additional GI benefit compared with ibuprofen and naproxen in patients receiving low-dose aspirin (75–100 mg/day) (Schnitzer et al. 2004b). Therefore, lumiracoxib is not expected to be cost effective in patients taking aspirin.

As detailed in the Current therapy options section, nonselective NSAIDs and the COX-2 inhibitors rofecoxib and celecoxib have been shown to increase BP. In patients with OA or RA, a 3 mmHg increase in SBP over 1 year was associated with a 4% increase in the incidence of ischemic heart disease and stroke events (Singh et al. 2003). A study estimating the clinical and economic impact of a 2.26% increase in SBP in 7.3 million American adults with OA and treated hypertension showed that maintaining BP control would avoid >30 000 deaths from stroke and 25 000 coronary deaths. This would theoretically result in >449 000 person-years of life saved and \$US1.4 billion in direct healthcare cost savings (Grover et al. 2005). Limited clinical evidence suggests that lumiracoxib does not increase the incidence of *de-novo* hypertension, and that lumiracoxib did not cause increased BP compared with patients receiving nonselective NSAIDs. The cost benefit of this potential reduction in CV events would be of interest. A clinical trial investigating the effect of lumiracoxib 100 mg once daily compared with ibuprofen 600 mg three times daily on ambulatory BP in patients with OA and controlled hypertension is currently underway (<http://www.clinicaltrials.gov>).

Patient group/population

Level 1 evidence from a Cochrane review of acetaminophen in OA concluded that the relative superiority of nonselective NSAIDs over acetaminophen is most marked in patients with moderate to severe levels of pain (Towheed et al. 2006). As acetaminophen is inexpensive and well tolerated it is likely that it will continue to be used as an initial therapy option for the initial treatment of patients with mild to moderate OA pain. In patients who fail to achieve adequate symptomatic relief with acetaminophen, nonselective NSAIDs are currently the preferred option, with COX-2 inhibitors used as an alternative, particularly in patients at high risk of developing serious GI adverse effects.

Patients with CV risk factors

It is currently recommended that all NSAIDs, including COX-2 inhibitors, are used with caution in patients with risk factors for CV disease such as hypertension, hyperlipidemia, diabetes, and smoking. However, a large proportion of patients with OA are likely to be elderly, and have CV risk factors or established CV disease.

The Third National Health And Nutrition Examination Survey (NHANES III) reported that over 47% of US adults with OA were older than 65 years of age and had a high prevalence of CV risk factors (Singh et al. 2002). Approximately 40% of individuals aged ≥ 35 years with OA had hypertension, 20% smoked, 11% had diabetes, and 32% had hypercholesterolemia. Therefore, a need remains for a COX-2 inhibitor that can be used safely in this high-risk population.

Data from TARGET demonstrate that lumiracoxib did not increase the incidence of MI, stroke, or other thrombotic CV events in patients that were treated for up to 1 year. This trial included patients with CV risk factors; 45% were hypertensive, 8% had diabetes, and 20% had dyslipidemia. Therefore, lumiracoxib may be used with caution in patients with these comorbidities (EMA 2005b). However, patients with established CV disease were excluded from TARGET.

Low-dose aspirin has a cardioprotective (antiplatelet) effect due to inhibition of the COX-1 enzyme. Therefore, it is prescribed to many patients with CV disease. Data from TARGET show that in patients receiving low-dose aspirin, lumiracoxib provided no benefit in ulcer complication reduction over ibuprofen or naproxen. Topol and Falk (2004) suggest that it is hard to justify the use of COX-2 inhibitors in these patients. In addition, NICE guidelines suggest that prescribing COX-2 inhibitors in combination with aspirin is not justified as they would not provide a GI benefit (NICE 2001).

Patients with hepatic impairment

Patients treated with lumiracoxib 400 mg experienced reversible elevations in liver function parameters. It is therefore likely that there is a low potential for lumiracoxib at the indicated dosage of 100 mg to increase the incidence of liver dysfunction in the outpatient setting. Liver function monitoring is advised before starting and every month during lumiracoxib treatment (MHRA 2007). The drug is contraindicated in patients with, or at high risk of, hepatic impairment (MHRA 2007).

Patients with renal impairment

NHANES III estimated that 37% of patients with OA have renal impairment, but fewer than 1% experience renal failure. Clinical evidence has shown that lumiracoxib is associated with a low incidence of peripheral edema. The summary of product characteristics states that under conditions of compromised renal perfusion, administration of lumiracoxib may impair renal function (EMA 2005b). Therefore, it is recommended that monitoring of renal function in these patients is considered.

Dosage, administration, and formulations

In the EU, lumiracoxib is indicated for symptomatic relief of OA at a recommended dose of 100 mg once daily. It is advised that the patients' need for symptomatic relief and response to therapy is reevaluated periodically. The summary of product characteristics advises that lumiracoxib is used with caution in patients most at risk of developing a GI complication with NSAIDs, and in patients with a history of cardiac failure, left ventricular dysfunction, hypertension, or preexisting edema. It warns that patients with significant CV risk factors should only be treated with lumiracoxib after careful consideration. Lumiracoxib is contraindicated in patients with current hepatic disease, previous drug-induced elevations of alanine aminotransferase (ALT)/aspartate aminotransferase (AST), ALT/AST >1.5 x upper limit of normal (ULN) before treatment or >3 x ULN during treatment, or taking other drugs that may impair hepatic function (MHRA 2007).

Clinical value

Clear evidence indicates that lumiracoxib is as effective as the nonselective NSAIDs diclofenac, naproxen, and ibuprofen, and the COX-2 inhibitor celecoxib for the management of pain in patients with OA, as shown by improvements in pain intensity and joint stiffness. Evidence suggests that lumiracoxib improves quality of life, as shown by improvements in WOMAC scores for the ability to perform daily activities and improvements in SF-36 scores for physical functioning and mental health. However, the economic impact of lumiracoxib on the treatment of OA, as compared to other currently available medications, has not been reported.

There is a need to identify the OA patient population most likely to benefit from COX-2 inhibitors as an alternative to nonselective NSAIDs. Evidence indicates that lumiracoxib is associated with a lower risk of upper GI complications, which is maintained for up to 1 year's treatment, compared with ibuprofen or naproxen. Patients already receiving aspirin would not have a GI benefit from treatment with lumiracoxib because of the inhibitory effects of aspirin on gastric COX-1. It is expected that lumiracoxib will be included in updated guidelines as an alternative therapy to nonselective NSAIDs in combination with PPIs, and as an alternative primary therapy to celecoxib in patients at high-risk of developing serious GI adverse effects. The impact of lumiracoxib on hospitalization and death rates resulting from GI complications compared to other NSAIDs has not been reported. Given the higher acquisition costs of lumiracoxib compared with nonselective NSAIDs, many of which are available generically, these data are important to evaluate any potential cost benefits.

There is moderate evidence that a high dose of lumiracoxib (400 mg) has a similar risk of CV events as ibuprofen and naproxen over a 1-year period. Further evidence will confirm if the CV safety is sustained in the longer term with approved doses (100 mg). The impact of lumiracoxib on CV events relative to other COX-2 inhibitors has not been reported. More

evidence is required to determine whether lumiracoxib has an advantage over other COX-2 inhibitors with regard to CV risk profile. In addition, the impact of lumiracoxib on CV events in patients with CV disease has not been reported. As the majority of patients with OA are aged ≥ 65 years, often have CV risk factors, and receive aspirin medication, more evidence evaluating the expected role of lumiracoxib in the management of these patients is needed.

The potential for adverse hepatic effects with lumiracoxib limit its usefulness. The drug was withdrawn from Australia in August 2007 following reports of serious adverse liver reactions (Therapeutic Goods Administration 2007), although this was at doses greater than the 100 mg approved in the EU. However, two cases of adverse liver reactions at this dose resulted in the drug being withdrawn in Canada in October 2007 (Health Canada 2007), and the drug has not been approved by the FDA because of concerns over its potential to impair liver function (Anon. 2007). In the EU, the drug is contraindicated in patients with current, or at risk from, hepatic dysfunction (MHRA 2007). The risk of adverse liver reactions appears to be small, with 11 case reports of severe reactions in the estimated 7 million patients who have taken the drug since it was introduced (MHRA 2007). Furthermore, the safety data reviewed by the FDA revealed that 0.85% of patients receiving lumiracoxib 100 mg for 12 months had ALT and AST elevations >3 x ULN, a rate considered to be similar to that seen with other NSAIDs (Anon. 2007).

In summary, lumiracoxib is a new COX-2 inhibitor providing an alternative treatment option for the management of OA, with comparable efficacy and CV safety to nonselective NSAIDs, but with a lower risk of GI complications in patients not taking aspirin. It may provide an acceptable risk-benefit balance in patients with a higher incidence of GI complications, including those with ulcers or being treated with anticoagulants.

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