Published in final edited form as:

Cochrane Database Syst Rev. ; (4): CD006865. doi:10.1002/14651858.CD006865.

Single dose oral lumiracoxib for postoperative pain

Yvonne M Roy¹, Sheena Derry², and R Andrew Moore²

¹Cochrane Pain, Palliative and Supportive Care Group, Pain Research Unit, Oxford, UK

²Pain Research and Nuffield Department of Anaesthetics, University of Oxford, Oxford, UK

Abstract

Background—Lumiracoxib is a novel selective cyclooxygenase-2 (COX-2) inhibitor. COX-2 inhibitors have been developed to avoid COX-1 related gastrointestinal (GI) problems. Lumiracoxib has analgesic and anti-inflammatory activity comparable with traditional non-steroidal anti-inflammatory drugs (tNSAIDs) in the management of post-operative pain, but with the advantage of better GI tolerability.

Objectives—To review the analgesic efficacy, duration of analgesia, and adverse effects of a single oral dose of lumiracoxib for moderate to severe postoperative pain in adults and compare it with established analgesics.

Search strategy—We searched CENTRAL (*The Cochrane Library* Issue 1, 2006), MEDLINE (1966 to March 2007), EMBASE (1974 to 2006), and PubMed (February 2007).

Selection criteria—Single oral dose, randomised placebo controlled trials of lumiracoxib, in acute postoperative pain, in adult patients.

Data collection and analysis—Trials were quality scored and data extracted by two review authors independently. Summed pain relief (TOTPAR) was extracted and converted into dichotomous information yielding the number of patients with at least 50% pain relief. These derived results were used to calculate the relative benefit (RB) and number-needed-to-treat (NNT) for one patient to achieve at least 50% pain relief.

Main results—Three studies (737 patients) met the inclusion criteria. In total 211 patients were treated with lumiracoxib 400 mg, 51 with lumiracoxib 100 mg, and 161 with placebo. Active comparators were naproxen 500 mg (60 patients), rofecoxib 50 mg (102), celecoxib 200 mg (101), and ibuprofen 400 mg (51). One hundred patients (48%) given lumiracoxib 400 mg had at least

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Contact address: Yvonne M Roy, Cochrane Pain, Palliative and Supportive Care Group, Pain Research Unit, The Churchill Hospital, Old Road, Oxford, OX3 7LJ, UK. yvonne.roy@pru.ox.ac.uk.

Editorial group: Cochrane Pain, Palliative and Supportive Care Group.

Publication status and date: Edited (no change to conclusions), published in Issue 1, 2009.

Review content assessed as up-to-date: 20 August 2007.

CONTRIBUTIONS OF AUTHORS

YMR: wrote the review, helped complete the search strategy, accessed papers, and obtained additional data for the review.

SD: data extraction, assistance in writing of the review, statistical and adverse event analysis.

RAM: conceived the idea for the review and helped with editorial and statistical analyses.

DECLARATIONS OF INTEREST

None known

50% pain relief over six hours, compared with 17 (11%) given placebo; RB 4.8 (95% CI 2.9 to 7.9), NNT 2.7 (2.2 to 3.5).

Weighted median time to use of rescue medication was 7.4 hours for lumiracoxib 400 mg and 1.8 hours for placebo. Patient global assessment at study endpoint was rated as “excellent” by 71 patients (34%) given lumiracoxib 400 mg and 5 (3%) given placebo.

Median time to onset of analgesia was shorter for lumiracoxib 400 mg (0.6 to 1.5 hours) than placebo (>12 hours), and use of rescue medication within 12 hours occurred in 64 patients (58%) given lumiracoxib 400 mg and 100 (91%) given placebo.

Adverse events reported were generally mild to moderate in severity, with one serious adverse event reported in a patient given placebo.

Authors’ conclusions—Lumiracoxib 400 mg given as a single oral dose, is an effective analgesic for acute postoperative pain.

Medical Subject Headings (MeSH)

Administration, Oral; Cyclooxygenase 2 Inhibitors [*administration & dosage]; Diclofenac [administration & dosage; *analogs & derivatives]; Pain, Postoperative [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans

BACKGROUND

Acute postoperative pain management is not always straightforward, and can often be poorly treated (Bruster 1994). Post-operative pain is particularly important as nearly 80% of patients report moderate-to-severe pain after surgery (Chan 2005). At present a variety of analgesic options are available which include traditional non-steroidal anti-inflammatory drugs (tNSAIDs) such as ibuprofen, naproxen and diclofenac. NSAIDs have pain-relieving, antipyretic and anti-inflammatory properties; and have proven efficacy following day surgery and minor surgery. Traditional NSAIDs may, however, cause gastric irritation, ulceration and perforation, especially with long term use, due to their non-selective inhibition of both the cyclooxygenase (COX) 1 and COX-2 isoforms of COX. Also, inhibition of COX 1 interferes with platelet aggregation, which may be of concern in the peri-operative setting (Chan 2005). Drug treatments that combine the pain-relieving properties of NSAIDs without these adverse effects would therefore be welcomed in clinical practice.

COX-2 inhibitors have been developed to avoid COX-1 related gastrointestinal (GI) problems. They have analgesic and anti-inflammatory activity comparable with tNSAIDs in the management of post-operative pain, but with the advantage of better GI tolerability (Benson 2000).

Lumiracoxib (Prexige®) is a novel selective COX-2 inhibitor with claimed improved biochemical selectivity over that of currently available coxibs (Mysler 2004). It is structurally distinct from other COX-2 selective inhibitors in that it has mildly acidic properties (pK_a 4.7). This acidity may be the reason for its distinct pharmacokinetic and pharmacodynamic profile, as weak acids have been shown to be readily sequestered into acidic environments such as inflamed joints (Day 1988). It is used for the symptomatic relief of osteoarthritis at 100 to 200 mg/day with clinical efficacy similar to that of diclofenac 150 mg/day and celecoxib 200 mg/day. Patients with rheumatoid arthritis benefit from a daily dose of 200 to 400 mg daily. Furthermore, it has been found to be effective for acute pain associated with primary dysmenorrhea, dental surgery and orthopaedic surgery, at a dose of 400 mg daily (Bannwarth 2005). Lumiracoxib is believed to be as effective as tNSAIDs but is thought to have superior gastrointestinal safety, especially in the reduction of ulcer complications (Schnitzer 2004a). There has been recent concern regarding the cardiovascular safety of some COX-2 inhibitors. Data from clinical trials and epidemiologic studies suggest that NSAIDs as a group may potentiate cardiovascular risk at some doses, whether they are selective for COX-2 or not (Scheiman 2005). Recent meta analyses of large observational studies suggest that cardiovascular risk is less of a class effect and more an effect of individual drugs (Hernandez-Diaz 2006; McGettigan 2006).

Oral lumiracoxib and intravenous (iv) parecoxib are currently the two coxibs licensed for postoperative pain management. Lumiracoxib over a short duration is likely to have a low risk of gastrointestinal and cardiovascular events and may therefore be a suitable and effective treatment for postoperative pain. Intravenous parecoxib followed by oral valdecoxib have been reported to have more frequent adverse effects after cardiac surgery (Nussmeier 2005; Ott 2003) but this is not the case after non-cardiac surgery (Nussmeier 2006).

Lumiracoxib is a new addition to the analgesic “list” and it is important to establish the efficacy of lumiracoxib compared to placebo and relative to established analgesics, in addition to its adverse event profile. This review aims to assess all the relevant available literature, to evaluate the efficacy and safety of lumiracoxib for the relief of postoperative pain.

As we go to press it has just been announced that Novartis has withdrawn lumiracoxib from the Australian market.

OBJECTIVES

To assess the analgesic efficacy, onset and duration of analgesia and adverse effects of a single oral dose of lumiracoxib for moderate to severe postoperative pain, and to compare its effectiveness with other analgesics used for treating acute pain.

METHODS

Criteria for considering studies for this review

Types of studies—Reports were included if they were published randomised placebo controlled, double blind trials of a single oral dose of lumiracoxib administered to patients experiencing moderate to severe postoperative pain.

Abstracts, review articles, case reports, and clinical observations were excluded, as were reports that did not clearly state that the interventions had been randomly allocated, were concerned with other pain conditions, or used experimental pain or volunteer participants, or both.

Types of participants—Male or female patients (aged 15 years and above) experiencing moderate to severe postoperative pain.

Types of interventions—Trials were included if they contained treatment groups allocated to a single oral dose of lumiracoxib or appropriate placebo that was administered to patients with established pain of moderate or severe intensity, which is defined as >3 on a 4 point categorical scale or >30 mm on a 100 mm Visual Analogue Scale (VAS), following an operative procedure.

Types of outcome measures

- Clinical outcomes include pain relief or pain intensity measured with categorical or VAS, to allow calculation of %maxTOTPAR and SPID at six hours where possible.
- Patient reported global assessment at study end point or withdrawal/remedication.
- Median time to onset of analgesia and use of rescue medication.
- Number of patients reporting any adverse event.
- Number of patients reporting any serious adverse event.
- Number of patients reporting withdrawing due to an adverse event.

Search methods for identification of studies

We searched the following databases:

- The Cochrane Central Register of Controlled Trials (CENTRAL) *The Cochrane Library* Issue 1, 2006;
- MEDLINE (1966 to February 2007);
- PubMed (March 2006);
- EMBASE (1974 to 2006);
- PaPaS Trials Register (February 2007).

Search strategies for MEDLINE, EMBASE and CENTRAL can be found in Appendix 1, Appendix 2 and Appendix 3 respectively.

Language—No language restriction was applied.

Additional sources—The authors of the included studies were contacted for additional numerical data, but none was supplied.

The manufacturer of lumiracoxib (Norvatis Pharmaceuticals Corporation) were contacted for further published or unpublished trials and abstracts.

Data collection and analysis

Electronic searches were carried out by RAM, YMR, and SD. Two review authors (YMR and SD) independently reviewed the titles and abstracts retrieved, and agreed upon the reports that would be retrieved in full for assessment for inclusion in the review. Disagreements were resolved by discussion.

Data management—Data were extracted by two review authors (YMR and SD) and recorded on a standard data extraction form. Data suitable for pooling were entered into RevMan 4.3.1

Data analysis—MeanTOTPAR was converted to %maxTOTPAR by division into the calculated maximum value (Cooper 1991). The proportion of patients in each treatment group who achieved at least 50%maxTOTPAR was calculated using verified equations (Moore 1996; Moore 1997a; Moore 1997b). These proportions were then converted into the number of patients achieving at least 50%maxTOTPAR by multiplying by the total number of patients in the treatment group. Information on the number of patients with at least 50%maxTOTPAR for active and placebo was then used to calculate relative benefit (RB) and number-needed-to-treat (NNT).

The number of patients who experienced at least 50% pain relief with lumiracoxib 400 mg, or placebo were entered into RevMan Analyses 4.3.1 and the RB (risk) estimates were calculated with 95% confidence intervals (CI) using a fixed effects model (Morris 1995). Number-needed-to-treat and number-needed-to-harm (NNT/NNH) and 95% CI were calculated by the method of Cook and Sackett (Cook 1995). A statistically significant difference from control was assumed when the 95% CI of the RB did not include one.

Adverse events—Methods used to collect adverse events were sought, together with the number of patients reporting adverse events for each treatment group, with the intention of calculating the number of participants who had:

- any adverse event,
- any serious adverse event,
- withdrawal due to an adverse event.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

The searches identified five studies. Of these, three studies met the inclusion criteria and were included in the review (Chan 2005; Kellstein 2004 and Zelenakas 2004). All three were funded by No-vartis Pharmaceuticals, the manufacturer of lumiracoxib and were identified as potential randomised controlled trials (RCTs) that assessed the effectiveness of lumiracoxib 400 mg in acute postoperative pain compared to placebo. The other two studies were not in postoperative pain and were excluded. The study by Bitner 2004 was a study on the treatment of primary dysmenorrhoea and the study by Schnitzer 2004 was in patients with knee or hip primary osteoarthritis.

Chan 2005 studied postoperative total knee or hip arthroplasty patients with moderate to severe pain. One hundred and eighty patients were recruited, 60 patients received 400 mg single dose lumiracoxib, 60 received 500 mg naproxen, and 60 received placebo. Kellstein 2004 studied postoperative dental patients, with third molar extractions who had moderate to severe pain. Three hundred and fifty five patients were recruited, 101 received lumiracoxib 400 mg, 102 received rofecoxib 50 mg, 101 received celecoxib 200 mg and 51 received placebo.

Zelenakas 2004 was also a postoperative dental surgery study, of third molar extraction for patients with moderate to severe pain. Two hundred and two patients were recruited. Fifty received lumiracoxib 400 mg, and 51 received lumiracoxib 100 mg, 51 received ibuprofen 400 mg and 50 received placebo.

Risk of bias in included studies

Each study that met the inclusion criteria was assessed independently for quality by two review authors (YMR and SD) using the three-item Oxford Quality Score (Jadad 1996b) and a score out of a maximum of five points was agreed. There was no disagreement between the review authors on quality scoring. These scores were not used to weight the results.

The scale used is as follows:

- is the study randomised? If yes, add one point;
- is the randomisation procedure reported and is it appropriate? If yes, add one point, if no, deduct one point;
- is the study double blind? If yes, add one point;
- is the double blind method reported and is it appropriate? If yes, add one point, if no, deduct one point;
- are the reasons for patient withdrawals and dropouts described? If yes, add one point.

The quality scores of the three included studies were:

Chan 2005, five (R2, D2, W1);

Kellstein 2004, three (R1, D2, W0);

Zelenakas 2004, four (R1, D2, W1).

Effects of interventions

Three studies met the inclusion criteria and provided data for this systematic review. Two studies (Kellstein 2004 and Chan 2005) assessed one 400 mg single dose of lumiracoxib. The other trial (Zelenakas 2004) assessed 400 and 100 mg doses. Data analysis was carried out on 211 patients who received lumiracoxib 400 mg, and the 161 patients who received placebo. For the Zelenakas 2004 trial of lumiracoxib 100 mg, only 51 received lumiracoxib and 50 placebo. Data analysis therefore was not carried out for lumiracoxib 100 mg as patient numbers were too small (Moore 1998).

Novartis Pharmaceuticals kindly supplied tables of pain relief over time for all three trials. Patient data was not available for one patient in each of the lumiracoxib 400 mg and placebo arms of the Chan 2005 study, although these patients completed the study. For this analysis we assumed that the missing data did not differ from the mean data provided. These data were used to calculate %maxTOTPAR and NNT for 50% pain relief over six hours. No study authors supplied any additional information.

Efficacy

Lumiracoxib versus placebo

>50% pain relief over six hours for lumiracoxib 400 mg versus placebo: Pain intensity was assessed using a four point categorical scale (none, mild, moderate, severe) in all three studies. These results were used to calculate the number of patients achieving at least 50% maxTOTPAR.

For Chan 2005, 20/59 (34%) patients had this outcome compared with 11/59 (19%) given placebo. For Kellstein 2004 the numbers were 48/101 (48%) and 0/51 (<1%) and for Zelenakas 2004 the numbers were 32/50 (64%) and 6/50 (12%). The NNT for one patient to achieve at least 50% pain relief over six hours for lumiracoxib 400 mg compared with placebo was 2.7 (95% CI 2.2 to 3.5) and the relative risk (RR) was 4.8 (95% CI 2.9 to 7.9). Data from the study by Zelenakas 2004 that assessed the 100 mg dose of lumiracoxib also showed some positive benefit compared to placebo, but this was a small trial where only 51 patients received the active treatment and it was felt patient numbers were too small to be included in the analysis for this review.

Time to onset of analgesia: The Chan 2005 study gave a time to onset of medication as 1.5 hours for lumiracoxib and >12 hours for placebo. Kellstein 2004 was 0.7 hours for lumiracoxib and >12 hours for placebo. Zelenakas 2004 was 0.6 hours for lumiracoxib and >12 hours for placebo.

Rescue medication: Median time to rescue medication was reported for all trials. For Chan 2005, it was 3.8 hours for lumiracoxib, compared with 2.0 for placebo. For Kellstein 2004 it was 7.2 hours for lumiracoxib compared with 1.3 hours for placebo, and for Zelenakas 2004 it was >12 hours for lumiracoxib compared with 2.0 hours for placebo. The weighted median time to rescue medication was 7.4 hours for lumiracoxib and 1.8 hours with placebo.

Two trials reported numbers of patients requiring rescue medication within 12 hours: Chan 2005, 42/60 (70%) given lumiracoxib and 54/60 (90%) given placebo, and for Zelenakas 2004 22/50 (44%) given lumiracoxib and 46/50 (92%) given placebo.

Patient global assessment: All studies used a four point scale (poor, fair, good and excellent). The numbers of patients reporting 'excellent' at 12 hours were 71/211 (34%) for lumiracoxib and 5/161 (3%) for placebo.

Lumiracoxib versus active comparators: There were insufficient data to allow direct comparison between lumiracoxib 400 mg and any individual active comparator. Using data from published meta-analyses we were able to make indirect comparisons (Smith 2001). The NNT for >50% pain relief at six hours for a single dose of lumiracoxib 400 mg compared to placebo in this review was 2.7, which compares with 2.4 for ibuprofen 400 mg, 2.3 for diclofenac 50 mg and 3.8 for paracetamol 1000 mg (Bandolier 2007).

Adverse events: One trial Chan 2005 appeared to report adverse events only at 96 hours, after a multiple dose phase, so provided no data for this analysis. Details of methods used to collect adverse events (spontaneous report, open question list) were not consistently reported. Two trials had information on numbers of patients with one or more adverse events. At 24 hours, Kellstein 2004 reported 21/101 patients with lumiracoxib 400 mg, and 9/51 with placebo (about 20%), while at 12 hours Zelenakas 2004 reported 1/50 (2%) with lumiracoxib 400 mg, and 10/50 with placebo (20%).

There was only one withdrawal due to an adverse event, in a patient given ibuprofen, who had postoperative bleeding at the suture site (Zelenakas 2004). There was no reported adjudication of relationship to the test drug. There was also only one serious adverse event, in a patient given placebo, who had a deep vein thrombosis (DVT) (Zelenakas 2004).

Adverse events were generally described as mild to moderate in severity, and were probably mostly related to the postoperative status of the patients. There was insufficient data for any pooled analysis.

DISCUSSION

The studies in this review are typical of acute pain studies, testing a single dose of analgesic or placebo in patients with established pain of moderate to severe intensity following dental or other surgical interventions, and measuring pain intensity, pain relief, time to onset of analgesia, numbers of patients requiring rescue medication and patient estimates of analgesic response.

Studies have typically used a four to six hour window to measure analgesic efficacy because that is the duration of effect for commonly used analgesics such as paracetamol, aspirin, ibuprofen and morphine. In addition, most studies (and those in this review) use “last observation carried forward” (LOCF) for missing data, for example when a patient uses rescue medication and provides no further efficacy measurements. This tends to overestimate efficacy compared with placebo, and the degree of overestimation increases with time as more patients use rescue medication, so that data for periods greater than six hours becomes unreliable (Moore 2005). Using “baseline observation carried forward” (BOCF) would give a more conservative estimate of efficacy.

We chose to combine the dental and orthopaedic studies, as systematic differences in analgesic efficacy between dental and post-surgical pain models have not been demonstrated and are considered unlikely (Barden 2004). Considering only clinically homogeneous dental studies, the corresponding NNTs were 2.1 (95% CI 1.8 to 2.7) for lumiracoxib 400 mg, which compares with 2.1 for ibuprofen 400 mg, 2.1 for diclofenac 50 mg, and 3.7 for paracetamol 1000 mg in dental patients (Edwards 2004).

Although we have a number of effective analgesics for use in post-operative pain management, in practice, pain control is often un-satisfactory because of inadequate remedication, that is, patients are not given pain medication when it is needed. A drug with a longer duration of action would limit the need to remedicate and potentially improve pain control. Time to use of rescue medication has become a useful indicator of efficacy for longer duration analgesics. In these trials the median time to use of rescue medication for placebo (1.8 hours) was consistent with that found in two meta-analyses (1.6 hours) (Edwards 2004; Moore 2005). Median time to rescue medication for lumiracoxib 400 mg (7.4 hours) was almost identical to ibuprofen 400 mg in the same meta-analyses (7.1 hours). With very similar results to ibuprofen, lumiracoxib could possibly be of use to patients who cannot tolerate ibuprofen.

There were insufficient data on adverse events to draw meaningful conclusions. Methods used to capture adverse events were incompletely described, and each trial reported for a different time period, making comparisons between trials or pooling of results impossible (Edwards 1999). Most of the adverse events reported were probably related to the postoperative status of the patient, and the only serious adverse event occurred in a patient given placebo. Using the “rule of three” we can estimate that a serious drug-related adverse event is unlikely to occur more frequently than once in about 70 patients (Eypasch 1995). Longer duration studies are more appropriate for determining adverse event profiles, particularly if time to event information is available.

In chronic use NSAIDs are effective as analgesics and anti-inflammatories, particularly in musculoskeletal pain, but they have a number of known adverse effects in chronic dosing. For example NSAIDs (and aspirin) are associated with upper gastrointestinal injury (Hernandez-Diaz 2000), acute renal failure (Griffin 2000; Henry 1997), congestive heart failure (GarciaRodriguez 2003; Page 2000) and myocardial infarction (Hernandez-Diaz 2006; Kearney 2006; McGettigan 2006) in long term studies. Less documented adverse

events include associations with increased fracture rates (Vestergaard 2006) and lower gastrointestinal injury (Adebayo 2006; Fortun 2005; Laine 2006).

The only expected benefit of coxibs over tNSAIDs is reduced levels of upper gastrointestinal bleeding. There is also, possibly, the benefit of lack of inhibition of platelet aggregation, but conclusive evidence in this area is poor. In practice, COX-2 inhibitors are differentiated from tNSAIDs by lower rates of upper and lower gastrointestinal harm, and possibly by lack of effect on bone. Any increased risk of myocardial infarction appears to be associated with individual drugs, rather than a class effect for tNSAIDs or COX-2 inhibitors (Hernandez-Diaz 2006; Kearney 2006; McGettigan 2006).

Presently, there are two new ongoing studies underway, looking at the efficacy of lumiracoxib in postoperative pain with Novartis Pharmaceuticals, Lumiracoxib(a) and Lumiracoxib(b) (see ongoing studies section). The data from these studies will in time add to the overall profile of lumiracoxib.

AUTHORS' CONCLUSIONS

Implications for practice

Based on limited evidence lumiracoxib 400 mg is as effective as ibuprofen 400 mg, both in terms of its NNT for at least 50% pain relief over six hours and for the duration of analgesia as measured by time to remedication.

Implications for research

We see no implications for research in the field of single dose acute pain studies. What is lacking are pragmatic studies determining how to ensure that patients achieve clinically relevant, say 50% pain relief, rather than exploratory studies which show that a drug is an analgesic.

In terms of adverse event profiles, this is difficult in a drug like lumiracoxib when it is used for short term use only. A possible approach might be to study time to event data in large trials of chronic use, although the study population is likely to differ.

Acknowledgments

Novartis Pharmaceuticals were contacted and kindly supplied information on two new ongoing trials. They also supplied additional data for the included studies.

I would like to thank Sylvia Bickley from the Pain Palliative and Supportive Care Review Group for her help and support with the search strategy.

SOURCES OF SUPPORT

Internal sources

- Oxford Pain Relief Trust, UK.

External sources

- No sources of support supplied

CHARACTERISTICS OF STUDIES

Characteristics of included studies [*ordered by study ID*]

Chan 2005

Methods	RCT, DB, DD, placebo and active controlled parallel-group study, 12 hour single dose phase, followed by multi-dose phase up to 96 hours for patients with moderate to severe pain	
Participants	Post operative total knee or hip arthroplasty surgery Male and females Age 18 to 80 years Mean age 64 years SD 11.0 N = 180	
Interventions	Lumiracoxib 400 mg n = 60 Naproxen 500 mg (2 × daily) n = 60 Placebo n = 60	
Outcomes	Patients with >50% PR over six hours: lumiracoxib 20/59, dplacebo 11/59 Time to remedication: Lumiracoxib 3.8 hours Placebo 2.0 hours Time to onset: Lumiracoxib 1.5 hours Placebo >12 hours	
Notes	QS = 5 (R2, D2, W1)	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Kellstein 2004

Methods	RCT, DB, DD, placebo and active controlled parallel group study, single oral dose with moderate to severe pain up to 24 hours	
Participants	Post-operative dental surgery, third molar extraction Male and females Age 17 to 41 years Mean age 22 years N = 355	
Interventions	Lumiracoxib 400 mg n = 101 Rofecoxib 50 mg n = 102 Celecoxib 200 mg n = 101 Placebo n = 51	

Outcomes	Patients with >50% PR over six hours: lumiracoxib 48/101, Placebo 0/51 Time to remedication: Lumiracoxib 7.2 hours Placebo 1.3 hours Time to onset: Lumiracoxib 0.7 hours Placebo >12 hours	
Notes	QS = 3 (R1, D2, W0)	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Zelenakas 2004

Methods	RCT, DB, DD, placebo and active controlled, parallel-group 12 hour study in patients with moderate to severe pain	
Participants	Post-operative dental surgery, third molar extraction Male and females Age >17 years Mean age 22 years SD 5.0 N = 202	
Interventions	Lumiracoxib 400 mg, n = 50, 100 mg n = 51 Ibuprofen 400 mg n = 51 Placebo n = 50	
Outcomes	Patients with >50% PR over six hours: lumiracoxib 32/50, Placebo 6/50 Time to remedication: Lumiracoxib >12 hours Placebo 2.0 hours Time to onset: Lumiracoxib 0.6 hours Placebo >12 hours	
Notes	One serious adverse event due to a DVT in a placebo patient QS = 4 (R1, D2, W1)	
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Key:

DB - Double blind

DD - Double Dummy

DVT - Deep vein thrombosis

PR - Pain relief

RCT - Randomised Controlled Trial

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Bitner 2004	Not post operative pain
Schnitzer 2004	Not post operative pain

Characteristics of ongoing studies [ordered by study ID]

Lumiracoxib(a)

Trial name or title	Efficacy of lumiracoxib in relieving moderate to severe post-dental surgery pain, compared to both placebo and celecoxib
Methods	
Participants	Male and females aged 17 years and over who require extraction of two or more partially impacted or fully bony impacted third molars. At least one of the extractions must be mandibular
Interventions	lumiracoxib 400 mg celecoxib 400 mg placebo
Outcomes	Superiority of a single dose of lumiracoxib 400 mg compared to placebo and celecoxib 400 mg based on a Summed (time weighted) Pain Intensity Difference calculated over 0-8 hours post-dose (SPID 8)
Starting date	February 2006
Contact information	
Notes	

Lumiracoxib(b)

Trial name or title	Efficacy and safety of lumiracoxib 400 mg in arthroscopic knee surgery
Methods	
Participants	Male and females 18 years and over who require minor ambulatory arthroscopic knee surgery
Interventions	lumiracoxib 400 mg placebo
Outcomes	Pain intensity in the target knee after movement at the 2 hour time point
Starting date	August 2006
Contact information	
Notes	

DATA AND ANALYSES

Comparison 1 Lumiracoxib versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 at least 50% pain relief at six hours	3	372	Risk Ratio (M-H, Fixed, 95% CI)	4.80 [2.91, 7.91]

Analysis 1.1 Comparison 1 Lumiracoxib versus placebo, Outcome 1 at least 50% pain relief at six hours.

Review: Single dose oral lumiracoxib for postoperative pain

Comparison: 1 Lumiracoxib versus placebo

Outcome: 1 at least 50% pain relief at six hours

Appendix 1. MEDLINE via OVID search strategy

1. Pain, Postoperative/
2. ((postoperative adj6 pain\$) or (post-operative adj6 pain\$) or post-operative-pain \$).mp. [mp=ti, ot, ab, nm, hw]
3. ((post-operative adj6 analgesi\$) or (postoperative adj6 analgesi\$)).mp. [mp=ti, ot, ab, nm, hw]
4. ((post-surgical adj6 pain\$) or ("post surgical" adj6 pain\$) or (post-surgery adj6 pain\$) or (post adj surg\$ adj pain\$)).mp. [mp=ti, ot, ab, nm, hw]
5. ((post\$ adj pain\$) or "pain relief after" or "pain following surg\$").mp. [mp=ti, ot, ab, nm, hw]
6. ((posttreatment adj6 pain\$) or ("pain control after" adj6 surg\$) or ((post-extraction or postextraction or post-surg\$) and (pain\$ or discomfort))).mp. [mp=ti, ot, ab, nm, hw]
7. (("analgesi\$ after" adj6 surg\$) or ("analgesi\$ following" adj6 surg\$) or ("analgesi\$ following" adj6 operat\$)).mp. [mp=ti, ot, ab, nm, hw]

8. ((analgesi\$ adj6 postoperat\$) or (analgesi\$ adj6 post-operat\$) or (pain\$ adj6 “after surg\$”) or (pain\$ adj6 “after operat\$”) or (analgesi\$ adj6 “after operat\$”)).mp. [mp=ti, ot, ab, nm, hw]
9. ((pain\$ adj6 “follow\$ operat\$”) or (analgesi\$ adj6 “follow\$ surg\$”)).mp. [mp=ti, ot, ab, nm, hw]
10. or/1-9
11. (lumiracoxib or prexige\$).mp. [mp=ti, ot, ab, nm, hw]
12. 10 and 11

Appendix 2. EMBASE search strategy

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((('lumiracoxib'/exp OR 'lumiracoxib') AND [embase]/lim) OR (prexige AND [embase]/lim)) AND (((('pain* AND 'following operation') OR (('analgesics'/exp OR 'analgesics') AND 'following surgery')) AND [embase]/lim) OR ('post surgery' AND pain* AND [embase]/lim) OR ('pain relief after' AND [embase]/lim) OR (postoperative AND analgesi* AND [embase]/lim) OR ('pain following' AND surg* AND [embase]/lim) OR (('postoperative pain'/exp OR 'postoperative pain') AND [embase]/lim)) AND [embase]/lim AND [embase]/lim)
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Appendix 3. CENTRAL search strategy

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#1 PAIN, POSTOPERATIVE
#2 ((postoperative NEAR/6 pain*) OR (post-operative NEAR/6 pain*)) OR post-operative-pain*
#3 ((post-operative NEAR/6 analgesi*) OR (postoperative NEAR/6 analgesi*))
#4 ((post-surgical NEAR/6 pain*) OR (,post surgical- NEAR pain*) or (post-surgery NEAR/6 pain*) OR post NEXT surg* NEXT pain*)
#5 ((post NEAR/6 pain*) OR ,pain relief after- OR (,pain following- NEAR/6 surg*))
#6 (( posttreatment NEAR/6 pain*) OR (,pain control after- NEAR/6 surg*) OR ((post-extraction OR postextraction OR post-surg*) AND (pain or discomfort))
((posttreatment NEAR/6 pain*) OR ,pain relief after- OR (,pain following- NEAR/6 surg*))
#7 ((,analgesi* after- NEAR/6 surg*) OR (,analgesi* following- NEAR/6 surg*) OR (,analgesi* following- NEAR/6 operat*))
#8 ((analgesi* NEAR/6 postoperat*) OR (analgesi* NEAR/6 post-operat*) OR (pain* NEAR/6 ,after surg*-) OR (pain* NEAR/6 ,after operat*-) OR (analgesi* NEAR/6 ,after operat*-))
#9 ((pain NEAR/6 ,follow* operat*-) OR (analgesi* NEAR/6 ,follow* surg*-))
#10 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11 lumiracoxib or prexige*
#12 #10 AND #11
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WHAT'S NEW

Last assessed as up-to-date: 20 August 2007.

Date	Event	Description
7 November 2008	Amended	Minor change to in-house referencing code

HISTORY

Review first published: Issue 4, 2007

Date	Event	Description
6 May 2008	Amended	Converted to new review format.
24 January 2008	Amended	On November 2007 the UK Medicines and Healthcare Regulatory Authority suspended the marketing authorisation for Lumiracoxib following safety concerns relating to liver damage in patients prescribed the drug for chronic/long term conditions such as osteoarthritis

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* Indicates the major publication for the study

PLAIN LANGUAGE SUMMARY

Single dose oral lumiracoxib (Prexige®) for treatment of postoperative pain relief in knee and hip arthroplasty and dental surgery

Postoperative pain is often poorly managed. Cyclooxygenase inhibitors (COX-2) pain relieving drugs were developed with the aim of reducing the gastrointestinal side effects of non-steroidal anti-inflammatory drugs (NSAIDs). Lumiracoxib, one of the latest COX-2 drugs to be developed, given in a 400 mg dose, appears to provide, rapid, effective and sustained relief of postoperative pain in three studies with a total of 737 participants. Two hundred and eleven patients were treated with lumiracoxib 400 mg and 100 of these patient (48%) had at least 50% pain relief over a six hour period, compared with 17 patients (11%) given placebo. Adverse event data was inconsistently reported, but no serious adverse events occurred in any patient taking lumiracoxib in these trials.