

NEW MEDICINES ON THE MARKET

Evaluated information for the NHS

PARECOXIB

Summary

- Parecoxib is the first selective cyclooxygenase-2 inhibitor for parenteral administration. It is licensed for the short-term treatment of post-operative pain.
- It has been shown to be comparable to treatment doses of ketorolac when administered after dental, orthopaedic and gynaecological surgery. In addition it has been shown to be efficacious when administered before dental surgery.
- Parecoxib has a morphine sparing effect, which has been demonstrated after gynaecological and orthopaedic surgery. However, it is not thought that concurrent use of parecoxib and morphine results in benefits to patients in terms of a reduction in the frequency or severity of opiate-related side effects.
- The commonest side effects in short-term use include dyspepsia, peripheral oedema, blood pressure changes, pruritus and oliguria. Studies of 7 day courses in healthy volunteers suggest that parecoxib causes fewer gastrointestinal ulcers and erosions and has a smaller effect on bleeding time than ketorolac. However, these benefits have not been demonstrated in a clinical setting.
- Parecoxib is an attractive alternative to parenteral ketorolac in the treatment of postoperative pain because of the potential for fewer gastrointestinal events and because it is not contraindicated in patients on heparin. There are no data for comparisons with other non-selective NSAIDs.
- However, parecoxib is relatively expensive compared to the alternatives and this, coupled with a lack of clinical trial data for its relative safety in short-term use in the clinical setting, means that its place in the management of postoperative pain is not yet clear.

Date Published: October 2002

Monograph Number: 4/02/04

Marketed: March 2002

Region of origin to whom enquiries should be directed: Leeds

The information contained in this document will be superseded in due course.

Not to be used for commercial purposes

Copyright MIPG 2002

Web site http://www.ukmi.nhs.uk/Med_info/stage4.html

PARECOXIB

Approved Name:	Parecoxib
Brand Name: (Manufacturer):	Dynastat (Pharmacia Limited)
Presentation:	20mg or 40mg powder and solvent for solution for injection
BNF Therapeutic Class:	Non-steroidal anti-inflammatory drugs (BNF 10.1.1)
Licensed Indications:	Indicated for the short-term treatment of postoperative pain in adults. Parecoxib has not been studied in patients under 18 years. Therefore, its use is not recommended in these patients.
Dosage and Administration:	40mg by IM or IV injection, followed every 6 to 12 hours by 20mg or 40mg as required to a maximum of 80mg per day.
Sector of Use:	Hospital [Y] Primary Care [N]

Therapeutic Comment:	Parecoxib is the first injectable COX-2 selective inhibitor. It appears to be comparable to ketorolac in terms of efficacy, with a superior safety profile. However, its effects on gastric mucosa and platelet function have yet to be fully examined in a clinical setting.
-----------------------------	---

Cost and Course Details:	Parecoxib 80mg daily £19.84 (for a 2 day course, from MIMS September 2002)
---------------------------------	---

Treatment Alternatives:	Cost of alternative parenteral NSAIDs, for 2 days: Diclofenac (Voltarol) 150mg daily: £3.30 Diclofenac (generic) 150mg daily: £2.96 Ketoprofen 200mg daily: £9.58 Ketorolac 90mg daily: £7.34 Lornoxicam 16mg daily: £9.00 (from MIMS September 2002)
--------------------------------	---

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used in the management of post-operative pain. NSAIDs inhibit cyclooxygenase (COX) enzymes, which are involved in the synthesis of prostaglandins and thereby reduce pain and inflammation. Oral NSAIDs are used post-operatively but when patients are unable to tolerate oral medications or require a faster onset of analgesia, parenteral administration may be preferred. Apart from parecoxib, the other parenteral NSAIDs available in the UK are diclofenac, ketoprofen, ketorolac and lornoxicam. All may be given intramuscularly, however this route of administration is often painful. Diclofenac, ketorolac and lornoxicam can be given intravenously, but diclofenac infusions must be buffered, which makes their preparation relatively complex. Ketorolac, which is licensed for a maximum of 2 days therapy, is contraindicated pre- and perioperatively [1] and is associated with gastrointestinal ulceration, renal impairment and increased perioperative bleeding, particularly in elderly subjects and with courses lasting longer than 5 days [2].

Parecoxib is a COX-2 selective inhibitor, which can be administered as an intravenous or intramuscular injection for the short-term management of postoperative pain.

PHARMACOLOGY

Cyclooxygenase (COX) exists in at least 2 distinct forms. COX-1 expression is ubiquitous and its activity predominates during normal physiologic conditions. It plays a key role in prostaglandin synthesis in the gastric mucosa, platelets and kidneys. Inhibition of COX-1 is associated with adverse gastrointestinal events and antiplatelet effects. COX-2 expression is restricted to a few locations (such as the brain and renal cortex)

during basal conditions. In response to stress, such as inflammation, COX-2 expression is markedly induced. Inhibition of COX-2 is thought to be primarily responsible for the anti-inflammatory and analgesic effects of NSAIDs. Traditional NSAIDs inhibit both the COX-1 and COX-2 isoenzymes. Parecoxib is one of a group of COX-2 selective NSAIDs, which have been developed with the aim of producing comparable pain control to traditional NSAIDs, with a reduced risk of serious adverse gastrointestinal and antiplatelet effects. Parecoxib is a water-soluble pro-drug that undergoes complete and rapid biotransformation to valdecoxib, a potent and selective inhibitor of COX-2 [3]. In vitro, the concentration of valdecoxib required for 50% inhibition of enzyme activity was over 25,000-fold lower for COX-2 than for COX-1 (0.005 versus 140 micromol/L) [3].

PHARMACOKINETICS

Following intravenous (IV) or intramuscular (IM) injection, parecoxib is converted to valdecoxib by enzymatic hydrolysis in the liver. Peak serum valdecoxib concentrations occur about 30 minutes after IV administration and 1 hour after IM injection. In clinical trials the first perceptible analgesic effect occurred in 7 to 13 minutes, with clinically meaningful analgesia demonstrated in 23 to 39 minutes and a peak effect within 2 hours following administration of single doses of 40mg by IV or IM injection [4].

Valdecoxib is metabolised extensively by the liver by multiple pathways, including cytochrome P450 3A4 and 2C9 isoenzymes. Less than 5% unchanged valdecoxib is recovered in urine. About 70% of the dose is excreted in the urine as inactive metabolites. The elimination half-life of valdecoxib is about 8 hours [4].

Dosage adjustment is recommended in elderly patients weighing less than 50kg and in patients with moderate hepatic impairment. No dosage adjustment is required

for patients with renal impairment, although caution is advised during use [4]. For further details, consult the SPC.

EFFICACY

Over 1,900 patients have received parecoxib (1 to 100mg) in clinical trials. Parecoxib has been evaluated in the treatment of acute pain after dental, gynaecological, orthopaedic and coronary artery bypass graft surgery. Key trials were of randomised, double-blind, parallel group and placebo-controlled design and each involving between 202 and 462 patients. Most trials [3, 5, 6, 8, 9, 11] had an active comparator. Parecoxib was generally given as a single IV or IM dose. Primary measures of most trials included pain intensity difference from baseline (PID), pain relief (PR), time to rescue medication and time to onset of analgesia. Other efficacy measures included patient global evaluation [6-9, 11-13], and cumulative amount of morphine used at 24 hours post-treatment with parecoxib or placebo [3, 5, 12, 13]. Many of the trials have yet to be published in full.

Dental surgery

In one of the few published studies, single doses of IV or IM parecoxib (20 or 40mg) demonstrated greater analgesic efficacy (measured by PID and PR) than placebo ($p \leq 0.05$) and similar efficacy to IM ketorolac 60mg when administered postoperatively in patients with dental pain. All the active treatments produced analgesia within 13 minutes. Parecoxib 40mg IV or IM had a longer duration of action than 20mg parecoxib or 60mg ketorolac [6]. Further details are presented in Table 1.

Further similar studies, available only in abstract form, confirm these findings [3, 5].

In another published study, patients were allocated a single IV dose of parecoxib (20mg, 40mg or 80mg) or placebo, administered 30 to 45 minutes before surgery.

The primary outcome was the time to rescue medication. Patients receiving parecoxib 40mg and 80mg required rescue medication significantly later than those given the 20mg dose (p values not given) [7]. Further details are presented in Table 1.

In summary, single doses of parecoxib were shown to be comparable to single doses of ketorolac in reducing pain following dental surgery [6]. In addition, parecoxib was shown to produce effective postoperative pain relief when given prior to surgery [7].

Orthopaedic surgery

Parecoxib has been evaluated in knee /hip replacement and foot surgery, however at the time of writing only one of these trials had been published in full [8].

Following knee replacement surgery, parecoxib 40mg IV was as effective as ketorolac 30mg IV and significantly more effective than morphine 4mg IV (all single doses, $p < 0.05$) as measured by PID and PR. Median time to onset of analgesia and median time to rescue medication were similar after parecoxib 40mg (11 minutes and 5.2 hours respectively) to those after ketorolac 30mg (12 minutes and 4.6 hours, no p values). Parecoxib was superior to IV morphine 4mg (median time to onset of analgesia, 15 minutes, median time to rescue medication, 2.1 hours, no p values), however this dose of morphine is lower than that commonly used in clinical practice. [5, 8].

Following total hip arthroplasty, parecoxib 20mg and 40mg IV and ketorolac 15mg IV, but not morphine 4mg IV, were superior to placebo with respect to the median time to rescue medication and patients global assessment of efficacy. There were no significant differences between the 2 doses of parecoxib and ketorolac [9]. For further details, refer to Table 1.

Preoperative administration of parecoxib was compared to placebo in patients undergoing hip or knee replacement or foot surgery. Patients received a single

IV dose of parecoxib 20mg or 40mg or placebo 30 to 45 minutes prior to surgery. Efficacy was measured by time to rescue medication and proportion receiving rescue medication. Except for the proportion of patients receiving rescue medication in the 20mg parecoxib arm, no significant benefit was shown over placebo. However, in a subset analysis, a significant difference with parecoxib 20mg and 40mg when compared to placebo in the time to rescue medication (7.1 hours and 10.7 hours versus 4.3 hours, $p < 0.001$) was observed in patients who underwent bunionectomy. In addition, the proportion of patients who required rescue medication in the parecoxib 20mg group was significantly lower than for placebo (65% versus 100%, $p \leq 0.05$) [5, 10].

Two separate studies carried out to a similar design investigated the opiate sparing effect of parecoxib in patients undergoing hip or knee replacement. Patients were randomised to placebo, parecoxib 20mg or parecoxib 40mg IV, given with the first dose of morphine. Patients self-administered morphine by patient-controlled analgesia. Further doses of study medication were given at 12 and 24 hours after the first dose. The primary efficacy endpoint was the amount of morphine consumed within 24 hours of the first dose of study medication. In the first study, in patients undergoing hip replacement, the differences in favour of active treatment were statistically significant ($p \approx 0.002$). In the second study, in patients undergoing knee replacement, only the difference between placebo and parecoxib 40mg IV was significant ($p < 0.001$). These two studies showed a morphine sparing effect allowing a 20 to 40% reduction in the dose of morphine [5]. Whilst it can be concluded that parecoxib and morphine can be safely used together, the reduction in morphine consumption did not appear to translate into a reduction in morphine-related side effects [5].

In summary, parecoxib was generally found to be comparable to ketorolac in orthopaedic surgery and to reduce the consumption of concurrent morphine in the postoperative period. However the Committee for

Proprietary Medicinal Products (CPMP) did not consider that the combined use of parecoxib and morphine reduced the severity or frequency of opiate-related side effects [5].

Gynaecological surgery

In one of the few published studies, intravenous parecoxib (20 or 40mg) was significantly more effective than placebo ($p \leq 0.05$) and as effective as IV ketorolac (30mg) at reducing pain intensity (PID) and providing pain relief (PR) following abdominal hysterectomy or myomectomy in 202 patients. Parecoxib 20mg provided comparable efficacy to the 40 mg dose across all variables measured. Median time to analgesia was similar among all active treatments (range 10 to 23 minutes). Median time to rescue medication was 6.2, 6.5 and 6 hours for parecoxib 20mg, 40mg and ketorolac 30mg respectively, which was significantly longer than that for IV morphine (2.6 hours) or placebo (1.8 hours, p values not reported) [5, 11].

Two further similar studies confirmed these findings [3, 5].

A study investigating the opiate sparing effect of parecoxib after gynaecological surgery demonstrated a significant difference in morphine consumption between IV parecoxib 20 or 40mg and placebo in patients who received study medication before the first dose of morphine and within 30 minutes of the end of surgery ($p \leq 0.05$) [12]. For details see Table 1. In a similar, published study parecoxib 20mg and 40mg significantly decreased patient-controlled morphine requirements at 12 (29 and 32%, $p < 0.05$) and 24 hours (33 and 35%, $p < 0.05$) compared with placebo in 55 female patients following major gynaecological surgery [13].

In summary parecoxib is comparable to ketorolac for the management of pain and reduces the consumption of morphine after gynaecological surgery [3, 5]. However, the CPMP did not consider that there was convincing benefit to the patient in terms of a reduction

in the severity or frequency of opiate-related side effects [5].

Coronary artery bypass grafting

A single, unpublished, multicentre study investigated the opiate sparing effects of parecoxib in patients undergoing coronary artery bypass grafting. Four hundred and sixty-two patients were randomised 2:1 to parecoxib/valdecoxib 40mg twice daily or placebo. All patients had access to morphine via patient controlled analgesia. After a minimum of 72 hours IV (parecoxib) was switched to oral (valdecoxib) treatment [5]. Differences in total morphine consumption were statistically significant for the first 72 hours. However when patients enrolled in Germany and the United Kingdom (where morphine consumption was lower) are removed the significance is lost [5].

ADVERSE EFFECTS

Over 3,500 healthy subjects received paracoxib or valdecoxib by the IV, IM or oral routes of administration. More than 1,900 patients received parecoxib (453 by the IM route) for post-surgical pain [4, 5]. About 65% of patients undergoing orthopaedic or gynaecological surgery received single doses [5]. In clinical trials, in patients treated with parecoxib 20mg or 40mg as a single or multiple dose (up to 80mg/day), the commonest adverse effects included blood pressure changes, back pain, peripheral oedema, dyspepsia, insomnia, postoperative anaemia, respiratory insufficiency, pruritus and oliguria. These effects were reported at an incidence of at least 1% [4, 5]. Further details are found in the SPC.

The discontinuation rate due to adverse events was 5.0% for patients receiving parecoxib and 4.3% for those on placebo [4]. There were no deaths or withdrawals from dental surgery studies due to adverse events. An 89 year old man who received parecoxib 20mg after orthopaedic surgery died from a stroke 9 days after study medication. In addition 4 of the 311

patients randomised to parecoxib 40mg bd and none of the 151 on placebo after coronary artery bypass surgery died. None of the deaths was attributed to test treatment by the study events committee, however 1 patient developed renal failure and 1 gastrointestinal bleeding as the initial event preceding death [5].

The upper gastrointestinal effects of parecoxib have been investigated in 2 published studies [14, 15]. The first randomised healthy elderly subjects to receive IV parecoxib 10mg bd, oral naproxen 500mg bd or placebo for 7 days or placebo for 2 days followed by IV ketorolac 15mg qds for 5 days. Among the first 17 subjects enrolled, ulcers were seen in all treatment groups except parecoxib. Due to the unexpectedly high incidence of gastroduodenal ulcers observed, the study was terminated early. These findings suggest that elderly patients may be at risk of ulcers even after short-term use of NSAIDs, however ulcers were reported in the placebo group. In addition, the dose of parecoxib used during this study is relatively low [14].

The second study enrolled 94 healthy elderly subjects who were randomised to receive IV parecoxib 40mg bd for 7 days, IV ketorolac 15mg qds for 5 days (preceded by 2 days of placebo) or placebo for 7 days. Gastric or duodenal ulcers did not occur in any subjects receiving parecoxib or placebo, nor did these subjects have more than 10 erosions. In contrast, 7 out of 31 (23%) subjects on ketorolac had at least 1 ulcer, and 8 (28%) had an ulcer or more than 10 erosions. In total, 28 (90%) ketorolac subjects had a gastric ulcer or at least 1 erosion, compared to 4 (14%) and 2 (6%) for parecoxib and placebo respectively [15]. It was concluded that repeated administration of parecoxib is safe and well tolerated in elderly subjects, with a decreased risk of gastroduodenal mucosal injury compared with ketorolac [15]. However it should be noted that the study enrolled healthy subjects who had not undergone surgery. In addition, ketorolac is licensed in the UK for a maximum of 2 days only [1].

The haemostatic effects of parecoxib were investigated in 2 trials, which compared the effects of parecoxib and ketorolac on platelet function and bleeding time in healthy volunteers [16]. The first study enrolled elderly subjects up to 83 years of age, who were randomised to receive IV parecoxib 10mg bd, IV parecoxib 40mg bd, IV ketorolac 15mg qds for 5 days (preceded by 3 days on placebo) or placebo for 8 days. During the course of this study it was determined that 10mg bd was not an effective dose, so individuals given this dose of parecoxib were not included in the analysis of platelet function. The second study was conducted in non-elderly subjects, who were randomised to IV parecoxib 40mg bd, IV ketorolac 30mg qds (for 5 days only) or placebo for 8 days [16]. Platelet function was assessed by the addition of platelet aggregation agonists, arachidonate, collagen and adenosine diphosphate (ADP). In addition measurements of bleeding time and serum thromboxane B₂ (Tx B₂) levels were carried out at set time points. In both studies, parecoxib had little or no effect on platelet aggregation, whilst ketorolac produced significant and sustained decreases in arachidonate-induced platelet aggregation in both age groups and in collagen-induced aggregation in the elderly subjects. Bleeding times were highly variable. The bleeding time in the ketorolac group of non-elderly subjects was significantly prolonged compared to parecoxib at 2 and 4 hours after the last dose. Parecoxib was similar to placebo. In all subjects ketorolac produced a profound reduction in Tx B₂ levels. The reduction in Tx B₂ levels in the parecoxib groups were not significantly greater than placebo except at 6 hours after the last dose in the elderly subjects [16]. These results indicate that parecoxib is less likely than ketorolac to be associated with excessive bleeding during or after surgery. However this has not been tested in a clinical setting.

CONTRAINDICATIONS AND PRECAUTIONS

Parecoxib is contraindicated in patients with active gastrointestinal bleeding or peptic ulceration, severe hepatic impairment, inflammatory bowel disease or severe congestive heart failure. In addition, it should not be used in patients who have experienced allergic type reactions to NSAIDs or other COX-2 selective inhibitors [4].

Caution is recommended following coronary artery bypass graft surgery because of a possible higher risk of adverse events [4, 5]. Inhibition of prostaglandin synthesis may result in deterioration of renal function and fluid retention; therefore parecoxib should be administered with caution in patients with renal failure. Further details of contraindications and precautions are available from the SPC [3].

It is recommended that anticoagulant therapy be monitored after initiating parecoxib in patients receiving warfarin because these patients have an increased risk of bleeding complications. Parecoxib has been shown not to affect the pharmacokinetics of co-administered heparin [4].

Fluconazole and ketoconazole have been shown to inhibit the metabolism of parecoxib. It is suggested that the dose of parecoxib should be reduced in patients on fluconazole. No dose adjustment is required for patients on ketoconazole. The effect of enzyme induction has not been studied but it is thought that the metabolism of valdecoxib may be affected by enzyme inducers such as rifampicin, phenytoin, carbamazepine or dexamethasone [4]. Valdecoxib has been shown to increase serum levels of dextromethorphan (CYP2D6 substrate) and omeprazole (CYP2C19 substrate) so caution is recommended in patients taking medicines known to be substrates of these isoenzymes. Co-administration of valdecoxib and lithium may result in an increase in lithium levels. Valdecoxib has been shown to have no effect on the pharmacokinetics or

pharmacodynamics of glibenclamide, propofol, midazolam, fentanyl or alfentanil [4].

REFERENCES

1. Toradol. Summary of Product Characteristics, Roche Products Ltd, 6th August 2001.
2. Dukes MNG (Ed). Meyler's Side Effects of Drugs, (14th Ed). Amsterdam: Elsevier Science Publishers, 2000.
3. Cheer SM & Goa KL. Parecoxib (parecoxib sodium). *Drugs* 2001; 61 (8): 1133-1141.
4. Dynastat. Summary of Product Characteristics, Pharmacia Europe EEIG, 22nd March 2002.
5. Dynastat. European Public Assessment Report (CPMP/1166/02). The European Agency for the Evaluation of Medicinal Products, London, 2002.
6. Daniels SE et al. A double-blind, randomized comparison of intramuscularly and intravenously administered parecoxib sodium versus ketorolac and placebo in a post-oral surgery pain model. *Clinical Therapeutics* 2001; 23 (7): 1018-1031.
7. Desjardins PJ et al. The injectable cyclooxygenase-2-specific inhibitor parecoxib sodium has analgesic efficacy when administered preoperatively. *Anesthesia and Analgesia* 2001; 93: 721-727.
8. Rasmussen GL et al. Intravenous parecoxib sodium for acute pain after orthopedic knee surgery. *The American Journal of Orthopedics* June 2002: 336-343.
9. Hubbard RC et al. The COX-2 specific inhibitor parecoxib sodium is effective in treating post-operative pain in total hip arthroplasty patients. *Anesthesiology* 2001; 95: A807 (abstract).
10. Hubbard RC et al. Preoperative administration of parecoxib sodium effectively reduces postoperative pain in bunionectomy patients. *American Society of Anesthesiologists 52nd Annual Meeting*, New Orleans, Louisiana, 13-17 October 2001 (abstract A-812).
11. Barton SF et al. Efficacy and safety of intravenous parecoxib sodium in relieving acute postoperative pain following gynecologic laparotomy surgery. *Anesthesiology* 2002; 97 (2): 306-314
12. Wender RH et al. Parecoxib sodium demonstrates opioid sparing effects in post-laparotomy surgical patients. *Fertility and Sterility* 2001; 76 (3, suppl 1): P325 (abstract).
13. Tang et al. Effect of parecoxib, a novel intravenous cyclooxygenase type 2 inhibitor, on the postoperative opioid requirement and quality of pain control. *Anesthesiology* 2002; 96 (6): 1305-1309.
14. Harris SI et al. Upper gastrointestinal safety evaluation of parecoxib sodium, a new parenteral cyclooxygenase-2-specific inhibitor, compared to ketorolac, naproxen and placebo. *Clinical Therapeutics* 2001; 23 (9): 1422-1428
15. Stolz RR et al. Upper GI mucosal effects of parecoxib sodium in healthy elderly subjects. *The American Journal of Gastroenterology* 2002; 97 (1): 65-71
16. Noveck RJ et al. Parecoxib sodium does not impair platelet function in healthy elderly and non-elderly individuals. Two randomised, controlled trials. *Clinical Drug Investigation* 2001; 21 (7): 465-476.

Table 1: Parecoxib in post-operative pain; summary of efficacy trials.

Ref No	Design of Study (Publication Type)	Treatments Assessed and Outcome Measures	Results and Comments															
6	<p>Dental surgery (postoperative use)</p> <p>Randomised, double-blind, double-dummy, placebo and active comparator-controlled, parallel group study. Mean age 21.8 yrs (n=304)</p> <p><u>Inclusion criteria:</u> Age between 18 and 64 years Removal of ≥2 third molars (≥1 of which was mandibular) requiring bone removal Moderate to severe pain within 6 hrs of surgery</p> <p><u>Exclusion criteria:</u> History of upper GI ulceration/bleeding in the previous 6 months Current significant upper GI complaint Ingestion of any drug which could confound the analgesic response in the 6 hrs before surgery Pregnancy</p>	<p>Pts allocated a single dose of one of the following after surgery: parecoxib 20mg IM (n=51), parecoxib 20mg IV (n=50), parecoxib 40mg IM (n=50), parecoxib 40mg IV (n=51), ketorolac 60mg IM (n=51) or placebo (n=51).</p> <p>Rescue analgesia (not specified) available. Pts encouraged to wait at least 60 minutes after receiving study medication.</p> <p><u>Primary outcomes:</u> Pain intensity difference from baseline (PID) Pain intensity (PI) on a 0-3 scale (0=none, 3=severe) and pain relief (PR) on a 0-4 scale (0=none, 4=complete); recorded by the pts at baseline (PI only), and at set times between 15 minutes and 24 hrs after administration of study medication. No further assessments of pain intensity/relief recorded after rescue medication.</p> <p><u>Secondary outcomes:</u> Times to perceptible pain relief and meaningful pain relief: recorded by each pt using a stopwatch. Global evaluation of study medication on a 1-4 scale (1=poor, 4=excellent) recorded 24 hrs after dosing or just before rescue medication.</p>	<p>Mean PID and PR scores for each treatment group were presented graphically.</p> <p><u>Pain Intensity difference and pain relief</u> Pts on all active treatments had significantly higher PID and PR scores than those on placebo (p≤0.05). The route of administration of parecoxib had no significant effect on mean PID scores. However, mean PR scores for parecoxib 40mg IM and IV were significantly higher than those for parecoxib 20mg IM and IV at 6, 9, 10, 11, 12 and 24 hrs (p≤0.05). The mean PID scores for ketorolac 60mg IM were higher than those for parecoxib 40mg IV from 45 minutes to 5 hrs after dosing (p≤0.05). Parecoxib 40mg IM produced higher mean PID scores than ketorolac from 12 to 24 hrs (p≤0.05). The differences in PR scores between ketorolac and parecoxib 40mg IV favoured ketorolac at 45, 60 and 90 minutes after dosing (p≤0.05). However, parecoxib 40mg IM was superior to ketorolac between 12 and 24 hrs and parecoxib 40mg IV was superior at 16 and 24 hrs (p≤0.05).</p> <p><u>Time to onset of analgesia</u> The median time to onset of analgesia was <13 minutes in all active treatment groups; there were no statistically significant differences.</p> <p><u>Time to use of rescue analgesia</u> The time to use of rescue medication was longer for parecoxib 40mg IM and IV than parecoxib 20mg IM and IV (21.7 hrs and 15.7 hrs versus 9.3 hrs and 7.1 hrs respectively, p≤0.05) and ketorolac 60mg IM (11.0hrs, p≤0.05).</p> <p><u>Global evaluation</u> All active treatments were considered more effective than placebo.</p>															
7	<p>Dental surgery (preoperative use)</p> <p>Double-blind, randomised, placebo-controlled, parallel group study. Mean age: 22.1 yrs (n=224)</p> <p><u>Inclusion criteria:</u> Age between 18 and 45 yrs The removal of 2 impacted third molars</p> <p><u>Exclusion criteria:</u> Similar to ref 6</p>	<p>Pts allocated a single intravenous dose of one of the following 30-45 minutes before surgery: parecoxib 20mg (n=56), parecoxib 40mg (n=56), parecoxib 80mg (n=56) or placebo (n=56).</p> <p>Rescue analgesia (various, including paracetamol, hydrocodone and pethidine) available at any time after surgery.</p> <p><u>Primary outcomes:</u> Median time to rescue medication.</p> <p><u>Secondary outcomes:</u> The proportion of pts needing rescue medication. Pain intensity (by visual analogue scale). Pts global assessment of study medication (as ref 6).</p>	<table border="1"> <thead> <tr> <th></th> <th>Parecoxib (20)</th> <th>Parecoxib (40)</th> <th>Parecoxib (80)</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>Median time to rescue med (hrs): (95% confidence intervals)</td> <td>6.3^A (4.1-11.2)</td> <td>>24^B (11.1->24)</td> <td>12.0^B (6.4-16.6)</td> <td>2.9^C (2.3-3.3)</td> </tr> <tr> <td>% pts taking rescue med:</td> <td>78‡§</td> <td>48†</td> <td>59†</td> <td>93</td> </tr> </tbody> </table> <p>(Treatments with the same capital letter are not significantly different (p values not quoted) ‡ p=0.031 vs. placebo, § p=0.03 vs. parecoxib 40mg, † p<0.001 vs. placebo)</p> <p>Global evaluation scores for all three parecoxib groups were significantly better than placebo (p<0.001).</p> <p>Ten pts were withdrawn, 9 for non-compliance with the study protocol and 1 for a violation of the entry criteria (2 from each of the placebo, parecoxib 40mg and 80mg groups and 4 from the parecoxib 20mg group).</p>		Parecoxib (20)	Parecoxib (40)	Parecoxib (80)	Placebo	Median time to rescue med (hrs): (95% confidence intervals)	6.3 ^A (4.1-11.2)	>24 ^B (11.1->24)	12.0 ^B (6.4-16.6)	2.9 ^C (2.3-3.3)	% pts taking rescue med:	78‡§	48†	59†	93
	Parecoxib (20)	Parecoxib (40)	Parecoxib (80)	Placebo														
Median time to rescue med (hrs): (95% confidence intervals)	6.3 ^A (4.1-11.2)	>24 ^B (11.1->24)	12.0 ^B (6.4-16.6)	2.9 ^C (2.3-3.3)														
% pts taking rescue med:	78‡§	48†	59†	93														

PARECOXIB

Ref No	Design of Study (Publication Type)	Treatments Assessed and Outcome Measures	Results and Comments																		
9 (Abs)	<p>Total hip arthroplasty (postoperative use)</p> <p>Double-blind, randomised, placebo and active comparator-controlled study. Mean age: 66 yrs (n=204)</p> <p><u>Inclusion and exclusion criteria:</u> not specified</p>	<p>Pts allocated a single dose of the following after surgery, within 6 hrs of discontinuation of patient controlled analgesia, when their pain intensity reached ≥ 45mm on the visual analogue scale: parecoxib 20mg IV, parecoxib 40mg IV, ketorolac 15mg IV, morphine 4mg IV or placebo.</p> <p>Rescue analgesia was available; no details are given.</p> <p><u>Outcomes:</u> Time to onset of analgesia. Time to rescue medication. Pain intensity and pain relief at scheduled time points (no details given).</p>	<p>Pts receiving parecoxib 20mg or 40mg or ketorolac 15mg experienced onset of pain relief in less than 13 minutes.</p> <table style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 60%;"></th> <th style="width: 20%; text-align: center;">Median time to rescue medication or remedication (hrs)</th> <th style="width: 20%; text-align: center;">Global evaluation of study medication (% pts scoring good or excellent)</th> </tr> </thead> <tbody> <tr> <td>Parecoxib (20)</td> <td style="text-align: center;">6.9‡</td> <td style="text-align: center;">88§</td> </tr> <tr> <td>Parecoxib (40)</td> <td style="text-align: center;">7.8§</td> <td style="text-align: center;">75§</td> </tr> <tr> <td>Ketorolac</td> <td style="text-align: center;">6.2†</td> <td style="text-align: center;">74§</td> </tr> <tr> <td>Morphine</td> <td style="text-align: center;">3.3</td> <td style="text-align: center;">37</td> </tr> <tr> <td>Placebo</td> <td style="text-align: center;">3.0</td> <td style="text-align: center;">25</td> </tr> </tbody> </table> <p>(† $p \leq 0.05$ vs. placebo, ‡ $p \leq 0.01$ vs. placebo, § $p < 0.001$ vs. placebo)</p>		Median time to rescue medication or remedication (hrs)	Global evaluation of study medication (% pts scoring good or excellent)	Parecoxib (20)	6.9‡	88§	Parecoxib (40)	7.8§	75§	Ketorolac	6.2†	74§	Morphine	3.3	37	Placebo	3.0	25
	Median time to rescue medication or remedication (hrs)	Global evaluation of study medication (% pts scoring good or excellent)																			
Parecoxib (20)	6.9‡	88§																			
Parecoxib (40)	7.8§	75§																			
Ketorolac	6.2†	74§																			
Morphine	3.3	37																			
Placebo	3.0	25																			
12 (Abs)	<p>Gynaecological surgery</p> <p>Double-blind, randomised, placebo controlled study (n= 216 women).</p> <p><u>Inclusion and exclusion criteria:</u> not specified</p>	<p>Pts randomised to study medication after surgery, to be given along with the first post-operative dose of morphine (1-2mg): parecoxib 20mg IV, parecoxib 40mg IV or placebo.</p> <p>Further doses of study medication were given at 12 and 24 hrs after the first dose. Morphine (1-2mg) by bolus or patient controlled analgesia, was available at any time.</p> <p><u>Primary outcomes:</u> Amount of morphine consumed within 24 hrs after surgery.</p> <p><u>Secondary outcomes:</u> Pt global evaluation of study medication.</p>	<p>In patients who received study medication within 30 minutes of the end of surgery and before the first dose of morphine, those on parecoxib 20mg or 40mg used 18% and 36% less total morphine than those given placebo ($p \leq 0.05$). In contrast, in the patients who received study medication after the first dose of morphine those on parecoxib did not consume significantly less morphine than those on placebo.</p> <p>In the patients global evaluation of study medication 96% pts given parecoxib 20mg, 95% pts given parecoxib 40mg and 84% pts given placebo (all in combination with morphine), rated their study medication as good or excellent.</p>																		