Rofecoxib
A Review of its Use in the Management of Osteoarthritis, Acute Pain and Rheumatoid Arthritis

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Data Selection
Sources: Medical literature published in any language since 1983 on rofecoxib, identified using Medline and EMBASE, supplemented by AdisBase (a proprietary database of Adis International, Auckland, New Zealand). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: Medline search terms were ‘rofecoxib’ or ‘MK 966’. EMBASE search terms were ‘rofecoxib’ or ‘MK 966’. AdisBase search terms were ‘rofecoxib’ or ‘MK-966’. Searches were last updated 4/04/2001.

Selection: Studies in patients with osteoarthritis, rheumatoid arthritis, postoperative dental pain, postoperative surgical pain or primary dysmenorrhoea who received rofecoxib. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: rofecoxib, osteoarthritis, rheumatoid arthritis, postoperative dental pain, postoperative surgical pain, primary dysmenorrhoea, pharmacodynamics, pharmacokinetics, therapeutic use.

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### Summary

**Abstract**

Rofecoxib is a selective cyclo-oxygenase (COX)-2 inhibitor which has little or no effect on the COX-1 isoenzyme at doses up to 1000 mg/day. Rofecoxib has greater selectivity for COX-2 than celecoxib, meloxicam, diclofenac and indomethacin.

In well-controlled clinical trials, rofecoxib 12.5 to 500 mg/day has been evaluated for its efficacy in the treatment of osteoarthritis, acute pain and rheumatoid arthritis [lower dosages (5 to 125 mg/day) were generally used in the chronic pain indications]. In the treatment of patients with osteoarthritis, rofecoxib was more effective in providing symptomatic relief than placebo, paracetamol (acetaminophen) and celecoxib and was similar in efficacy to ibuprofen, diclofenac, naproxen and nabumetone. Overall, both the physician’s assessment of disease status and the patient’s assessment of response to therapy tended to favour rofecoxib. In patients with postsurgical dental pain, pain after spinal fusion or orthopaedic surgery, or primary dysmenorrhoea, rofecoxib provided more rapid and more sustained pain relief and reduced requirements for supplemental morphine use after surgery than placebo. Rofecoxib was more efficacious than celecoxib in patients with acute dental pain and pain after spinal fusion surgery, although celecoxib may have been used at a subtherapeutic dose. In comparison with traditional nonsteroidal anti-inflammatory drugs (NSAIDs) ibuprofen, diclofenac and naproxen sodium, rofecoxib was similar in efficacy in the treatment of acute pain. Although naproxen sodium provided more rapid pain relief than rofecoxib in patients with primary dysmenorrhoea, the reverse was true after orthopaedic surgery: rofecoxib provided more rapid pain relief and less supplemental morphine was needed. Rofecoxib was as effective as naproxen in providing symptomatic relief for over 8700 patients with rheumatoid arthritis.

Compared with traditional NSAID therapy, rofecoxib had a significantly lower incidence of endoscopically confirmed gastroduodenal ulceration and, in
approximately 13,000 patients with osteoarthritis and rheumatoid arthritis, a lower incidence of gastrointestinal (GI) adverse events. Rofecoxib was generally well tolerated in all indications with an overall tolerability profile similar to traditional NSAIDs. The most common adverse events in rofecoxib recipients were nausea, dizziness and headache.

In conclusion, rofecoxib is at least as effective as traditional NSAID therapy in providing pain relief for both chronic and acute pain conditions. Rofecoxib provides an alternative treatment option to traditional NSAID therapy in the management of symptomatic pain relief in patients with osteoarthritis. Initial data from patients with primary dysmenorrhoea and postoperative pain are promising and further trials may confirm its place in the treatment of these indications. Rofecoxib has also shown promising results in patients with rheumatoid arthritis and is likely to become a valuable addition to current drug therapy for this patient population. Importantly, rofecoxib is associated with a lower incidence of GI adverse events than traditional NSAIDs making it a primary treatment option in patients at risk of developing GI complications or patients with chronic conditions requiring long term treatment.

**Pharmacodynamic Profile**

Rofecoxib is a selective and potent cyclo-oxygenase (COX)-2 inhibitor both in vitro and in vivo. In vitro, concentrations of rofecoxib required to inhibit COX-2 by 50% (IC50) were 0.018 to 0.046 μmol/L; there was no appreciable effect on the COX-1 isoenzyme. In 25 healthy volunteers, the IC50 value for inhibition of COX-2 activity by rofecoxib 25 to 1000 mg was 0.77 μmol/L; in contrast, the IC50 value for indomethacin 5 to 75 mg was 0.3 μmol/L. There was no significant inhibition of COX-1 with rofecoxib; the indomethacin IC50 for COX-1 was 0.09 μmol/L. In vitro rofecoxib has a higher selectivity ratio (COX-1 IC50/COX-2 IC50) for COX-2 inhibition than celecoxib, meloxicam, diclofenac and indomethacin.

It has also demonstrated analgesic and antipyretic effects in 94 patients with fever caused by an upper respiratory tract infection (URTI) or suspected benign systemic viral infection. Single doses of rofecoxib 12.5 or 25 mg or ibuprofen 400 mg significantly reduced body temperature within 1 to 1.5 hours and 30 minutes of administration, respectively, compared with placebo. Similar results have been demonstrated in animal models of inflammation, pain and fever.

Rofecoxib treatment had less effect on the gastrointestinal (GI) mucosa than aspirin, naproxen, ibuprofen and indomethacin. In 24 healthy volunteers, gastric mucosal prostaglandin E2 (PGE2) synthesis was increased 18% by rofecoxib 50 mg/day and decreased 65% by naproxen 500 mg twice daily; in turn, COX-2 dependent lipopolysaccharide PGE2 production was inhibited by approximately 80% for both. Serum thromboxane (TXB2) generation (a measure of COX-1 activity) was unaffected by rofecoxib and inhibited by 94% with naproxen. Intestinal permeability was 3-fold higher with indomethacin 150 mg/day than with rofecoxib 25 or 50 mg/day or placebo. GI microbleeding was associated with ibuprofen 2400 mg/day treatment resulting in a higher rate of faecal blood loss than with rofecoxib 25 or 50 mg/day (2 vs 1 ml/day) in 67 healthy volunteers.

Rofecoxib had no effect on TXB2 inhibition or the anti-platelet activity of low-dose aspirin in an ex vivo study in 24 healthy volunteers. Likewise in vitro, rofecoxib had no effect on TXB2 production by calcium ionophore-challenged human platelets.

**Pharmacokinetic Profile**

After oral administration, single 12.5 or 25 mg doses of rofecoxib are well ab-
sorbed, reaching maximum plasma concentrations (C\text{max}) of approximately 207 \mu g/L 2 to 3 hours after administration of rofecoxib 25mg. A steady-state C\text{max} of 321 \mu g/L was reached within 4 days. The mean oral bioavailability of a 12.5 to 50mg dose was 93%. If rofecoxib is administered with food, the time to reach C\text{max} is delayed by 1 to 2 hours.

At concentrations of 0.05 to 25 mg/L, rofecoxib is largely bound to plasma proteins (87%); tissue distribution has not yet been characterised in humans. Radioactively labelled rofecoxib is extensively metabolised within the liver to 2 inactive \textit{cis}-dihydro and \textit{trans}-dihydro metabolites which together account for approximately 56% of radioactivity recovered in the urine. The elimination half-life of rofecoxib is approximately 17 hours. Elimination occurs via hepatic metabolism with <1% of a rofecoxib dose excreted unchanged in the urine. Approximately 14% of a single 125mg radiolabelled dose of rofecoxib was excreted unchanged in the faeces.

In those aged \(\geq 65\) years, oral administration of rofecoxib 25mg results in a 34% increase in the area under the plasma concentration-time curve (AUC) compared with younger adults; while dosage adjustment is not necessary, treatment should be initiated at the lowest possible dose in these patients. Absorption is also decreased when rofecoxib is administered concurrently with calcium carbonate or magnesium/aluminium antacids in this patient group.

Limited data are available on the pharmacokinetics of rofecoxib in patients with renal or hepatic impairment. The AUC was increased by 69% in 4 individuals with moderate hepatic impairment compared with 4 healthy individuals. There are currently no data on patients with severe hepatic impairment. In 6 patients with end-stage renal failure undergoing dialysis 4 hours after the administration of rofecoxib, C\text{max} and AUC were decreased by 18 and 9%, respectively. To date there are no data on the effects of rofecoxib in advanced renal disease; therefore rofecoxib is not recommended in these patients.

Concurrent administration of rofecoxib and oral prednisone or intravenous prednisolone had no clinically significant effects on the pharmacokinetics of prednisone or prednisolone. Likewise, serum concentrations of digoxin, ethinylestradiol and norethindrone were unaffected by coadministration of rofecoxib. In patients with rheumatoid arthritis, the addition of rofecoxib 12.5, 25 or 50mg to a stable methotrexate regimen (7.5 to 15 mg/week) had no clinically significant effect on methotrexate plasma concentrations. The plasma concentration of rofecoxib 75 mg/day was increased and the renal clearance of methotrexate 7.5 to 15 mg/week was decreased when these drugs were coadministered at these dosages. When rofecoxib is coadministered with either warfarin or rifampicin, patients should be monitored for potential interactions.

Rofecoxib is more effective than placebo, paracetamol (acetaminophen), nabumetone or celecoxib and is generally as effective as the traditional NSAIDs ibuprofen, naproxen (or naproxen sodium) or diclofenac in the treatment of osteoarthritis or acute pain. It has shown promising results compared with naproxen in patients with rheumatoid arthritis.

**Osteoarthritis.** In the treatment of osteoarthritis, rofecoxib 12.5 to 125 mg/day for 6 weeks was significantly more effective than placebo in improving pain compared with baseline values as assessed by the Western Ontario McMasters Universities Osteoarthritis Index (WOMAC) and the patient’s assessment of arthritic pain.
In comparative trials with other NSAIDs, pain when walking showed a significantly greater improvement with rofecoxib 12.5 or 25 mg/day than with celecoxib 200 mg/day or paracetamol 1000 mg/day. Furthermore, rofecoxib was similar in efficacy when compared with ibuprofen 2400 mg/day, diclofenac 150 mg/day or naproxen 1000 mg/day. Patient assessment of response to therapy, physician global assessment of disease status and the WOMAC pain subscale scores were also similar for rofecoxib and diclofenac but the 2 former scales showed slightly greater improvement with rofecoxib compared with ibuprofen; reaching significance in 1 study. Data from 1 study show that diclofenac was significantly better than rofecoxib for patient assessment of response to therapy, physician global assessment of disease status and patient global assessment of disease status. Joint space narrowing, signifying disease progression, decreased in over 700 patients receiving rofecoxib 12.5 or 50 mg/day and diclofenac in two 1-year trials.

**Postsurgical dental pain.** Postsurgical dental pain was relieved more rapidly, and at 8 hours after administration of the study drug, total pain relief was greater, with single doses of rofecoxib 12.5 to 500mg than with either placebo or a single dose of celecoxib 200mg. Single doses of rofecoxib and ibuprofen 400mg had similar effects on these measures. A longer duration of analgesic effect and less need for rescue medication 24 hours after drug administration was also seen with rofecoxib recipients compared with placebo, ibuprofen or celecoxib. Single 50 and 500mg doses of rofecoxib were not significantly different with respect to total pain relief scores at 8 hours, although rofecoxib 50mg showed significantly better efficacy than 12.5 but not 25mg. However, comparisons between rofecoxib and celecoxib must be interpreted cautiously because celecoxib was given at doses recommended for osteoarthritis, which may have been subtherapeutic in this indication.

**Postoperative surgical pain.** Rofecoxib 50mg was effective in relieving acute pain in patients who had spinal fusion or orthopaedic surgery. Compared with celecoxib 200mg and placebo, rofecoxib recipients who had spinal fusion surgery had significantly lower verbal analogue pain scores (VbAS) at 12 and 16 hours postoperatively ($p < 0.03$). Rofecoxib VbAS scores remained numerically lower than placebo or celecoxib recipients up to 20 hours postoperatively. In addition, rofecoxib recipients required significantly less supplemental morphine than celecoxib or placebo recipients. Again, caution must be exercised in interpreting comparative data for rofecoxib and celecoxib, since subtherapeutic doses may have been used. In the treatment of 218 patients who underwent orthopaedic surgery, rofecoxib 50mg provided significantly greater pain relief up to 8 hours postoperatively than placebo and similar pain relief compared with naproxen sodium 550mg. However, compared with both naproxen sodium and placebo, rofecoxib provided a more rapid onset of pain relief and less supplemental morphine was required. There were no differences between rofecoxib 50mg and placebo in terms of visual analogue scale scores, patient assessment of overall pain relief or supplemental morphine use in the treatment of radical prostectomy in a small study.

**Primary dysmenorrhoea.** In patients with primary dysmenorrhoea, rofecoxib 25 or 50mg was similar in efficacy to naproxen sodium 550mg and significantly better than placebo for providing pain relief up to 8 hours after the onset of moderate to severe pain. Patient evaluation of the study drug favoured rofe-
coxib when compared with placebo (p ≤ 0.006); patient preference was similar for rofecoxib and naproxen sodium. However, time to actual pain intensity difference relative to baseline was shortest for naproxen sodium (1 hour vs 1.5 hours for rofecoxib and placebo (p ≤ 0.006). A significantly greater proportion of placebo than either rofecoxib or naproxen sodium recipients required rescue medication and took extra doses of study medication within 12 hours of pain onset (p ≤ 0.006).

**Rheumatoid arthritis.** After a median of 9 months, rofecoxib 50mg once daily had similar efficacy compared with naproxen 500mg twice daily for improvements in global disease activity and investigator assessment of efficacy in over 8000 patients with rheumatoid arthritis. There were no statistically or clinically significant differences between rofecoxib and naproxen in the improvement in the Modified Health Assessment Questionnaire score compared with baseline. In a smaller study (n = 658), rofecoxib 25 and 50mg were significantly better than placebo in achieving a 20% improvement in various American College of Rheumatology parameters after 8 weeks of therapy. The results held for individual efficacy measurements and were maintained 1 year after the initiation of therapy. Co-administration of methotrexate had no significant effect on either treatment.

**GI Adverse Events.** The incidence of withdrawal because of a GI adverse event (perforations, ulcerations and bleeding; PUB) was lower for rofecoxib (3.5%) than for traditional NSAIDs ibuprofen, diclofenac or nabumetone (4.8%), according to the results of a meta-analysis of 8 double-blind randomised studies including a total of over 5000 patients with osteoarthritis. Furthermore, a significant difference between rofecoxib and the traditional NSAIDs in the incidence of PUBs was evident as early as 6 weeks (p = 0.004). At 12 months, the rate per 100 patient-years for GI adverse events was significantly lower with rofecoxib (p = 0.01). Endoscopy confirmed the lower incidence of GI ulceration ≥3mm and ≥5mm with rofecoxib treatment 25 or 50 mg/day than with ibuprofen 2400 mg/day (p < 0.001).

A lower overall incidence of confirmed upper GI events was reported with rofecoxib (1.4%) than with naproxen (3%) in over 8000 patients with rheumatoid arthritis enrolled in the VIGOR (VIOXX Gastrointestinal Outcomes Research) study. The relative risk (RR) of a confirmed upper GI event for rofecoxib versus naproxen was 0.5 (p < 0.001). The RR of a complicated confirmed upper GI event was 0.4 (p = 0.005). Similarly the RR of complicated upper GI bleeding and bleeding beyond the duodenum was 0.4 (p = 0.004) and 0.5 (p = 0.03), respectively.

**Cardiovascular Adverse Events.** In the VIGOR study, the mortality rates in over 8000 patients with rheumatoid arthritis were comparable with rofecoxib and naproxen (0.5 vs 0.4%). The mortality rate from cardiovascular causes was 0.2% for both treatment groups. However, the incidence of myocardial infarctions was higher for rofecoxib (0.4 vs 0.1% with naproxen); within this group, 38% of those who had a myocardial infarction were eligible for aspirin as a secondary prophylaxis but were not receiving this therapy. When these patients were excluded from the analysis, the incidence of myocardial infarction was 0.2% for rofecoxib and 0.1% for naproxen. A lower incidence of thromboembolic cardiovascular events was reported with rofecoxib 12.5 and 25mg than with diclofenac 150 mg/day in a 1-year study of 784 patients with osteoarthritis.
**General Tolerability Profile.** Rofecoxib was generally well tolerated in the clinical trials of patients with osteoarthritis, acute pain or rheumatoid arthritis. In patients with osteoarthritis, adverse events reported with a higher incidence with rofecoxib 25 or 125 mg/day than with placebo, included URTI (9.6 and 13.5% for rofecoxib 25 and 125mg vs 5.6% for placebo) headache (5.5 and 12.2 vs 6.9%), viral syndrome (6.8 and 4.1 vs 1.4%) and sinusitis (4.1 for both rofecoxib doses vs 2.8%). Likewise URTI, sinusitis and heartburn were reported with a higher incidence with rofecoxib 12.5 or 25 mg/day than with diclofenac 150 mg/day, although these differences were not significant. However, a lower incidence of URTI (2.9 for rofecoxib vs 5% for diclofenac/misoprostol), abdominal pain (8.7 vs 13.3%), diarrhoea (6.2 vs 19.9%), dyspepsia (2.9 vs 10.8%), epigastric discomfort (3.7 vs 11.2%), headache (5.8 vs 9.5%) and nausea (8.3 vs 10.4%) were associated with rofecoxib 12.5 mg/day than with diclofenac/misoprostol (50mg/200μg twice daily). A lower incidence of epigastric discomfort and a similar incidence of diarrhoea were reported with rofecoxib 12.5 or 25 mg/day compared with ibuprofen 800mg 3 times daily. However, a higher incidence of nausea was associated with rofecoxib 25mg.

In the treatment of postsurgical dental pain, rofecoxib 50 mg/day was generally associated with a lower incidence of nausea, headache and vomiting compared with placebo, ibuprofen 400 mg/day and celecoxib 200 mg/day.

In patients with postoperative surgical pain, constipation, nausea and fever were the most commonly reported adverse events with rofecoxib 25 or 50mg therapy. Rofecoxib 25 or 50 mg/day was associated with a lower incidence of constipation than either placebo or naproxen sodium 550 mg/day; a higher incidence of nausea was noted with rofecoxib 50 mg/day than with naproxen sodium or placebo and there was a higher incidence of fever with rofecoxib 50 mg/day compared with naproxen.

Nausea and dry mouth were the most commonly reported adverse effects associated with rofecoxib 25 or 50mg in the treatment of primary dysmenorrhoea. In these patients a higher proportion of rofecoxib recipients experienced an adverse event compared with placebo or naproxen sodium 550mg recipients.

The most common adverse events occurring in patients with rheumatoid arthritis were diarrhoea, headache, fatigue and dizziness. The incidences of headache and fatigue were lower with rofecoxib than placebo. The incidences of lower extremity oedema were low and were similar between the treatment groups.

There are few formal data on the pharmacoeconomics of rofecoxib. In patients with osteoarthritis, rofecoxib has a slightly higher acquisition cost per patient than other commonly used NSAIDs ($1.60 vs 1.67 per day, Canadian (Can) dollars), leading to an incremental annual cost of $24.45 per patient using rofecoxib. Higher costs may be attributed to patients using rofecoxib in the treatment of acute pain, because higher dosages are generally used for this indication. On the other hand, however, rofecoxib is associated with a reduction of 0.0109 PUBs per patient per year which translates into costs per PUB averted of $Can2247.

In patients with rheumatoid arthritis and a high risk of developing NSAID-induced GI complications, 40 patients would need to be treated with rofecoxib to prevent 1 ulcer complication (assuming rofecoxib reduced the risk by 50%); this equates to a yearly incremental cost of $US30 000 based on 1999 US data comparing rofecoxib 25 mg/day with a generic NSAID such as naproxen. More than 500 patients with rheumatoid arthritis and a low risk of developing an NSAID-
induced GI complication would need to be treated to prevent 1 ulcer (based on similar assumptions) at a yearly incremental cost of US$400 000.

Dosage and Administration

In the US, rofecoxib is approved for the treatment of osteoarthritis and acute pain including dental pain, postsurgical pain and primary dysmenorrhea in adults. It is available in tablet form 12.5 or 25mg or as a suspension 12.5 or 25mg in 5ml. For patients with osteoarthritis, the recommended initial dose is 12.5 mg/day; this dose may be increased up to a maximum of 25 mg/day. For the treatment of acute pain, the recommended initial daily dosage is 50mg and 50mg may be given on subsequent days as needed. Doses of up to 1000mg have been evaluated in clinical trials; however, there are few tolerability data at this dose level. Rofecoxib can be administered with or without food.

Physicians and patients should be alert for ulceration and bleeding even in the absence of previous GI symptoms. Rofecoxib is not recommended in patients with moderate or severe hepatic impairment, advanced kidney disease, pre-existing asthma, aspirin-sensitive asthma, hypersensitivity to rofecoxib or at a late stage in pregnancy. Patients using rofecoxib long term should be monitored for the development of hypertension and oedema and have their haemoglobin or haematocrit checked if they exhibit signs or symptoms of anaemia or blood loss. Caution should be used in patients with hypertension or heart failure.

Caution should be used when coadministering rofecoxib with ACE inhibitors, rifampicin, warfarin, methotrexate, lithium and aspirin. Coadministration of rofecoxib with either cimetidine or ketoconazole did not have any clinically significant effect on the pharmacokinetics of rofecoxib.

1. Selective COX-2 Inhibitors

Treatment for osteoarthritis, rheumatoid arthritis and acute pain has primarily relied on traditional nonsteroidal anti-inflammatory drugs (NSAIDs) such as naproxen, diclofenac and ibuprofen, which have been associated with potentially serious gastrointestinal (GI) complications.[1,2] The unwanted GI adverse effects associated with these agents are thought to result from the inhibition of the cyclooxygenase (COX)-1 isoenzyme involved in prostaglandin synthesis.[3,4] The therapeutic effects are thought to largely be the result of the inhibition of the COX-2 isoenzyme.[5] COX-2 selective agents are being developed to capitalise on the favourable effects of selective COX-2 inhibition. For recent and comprehensive reviews of COX inhibition and prostaglandin synthesis see Cannon[3] or Clemett and Goa.[6]

Two recently developed COX-2 selective agents are rofecoxib (fig. 1) and celecoxib.[3] Rofecoxib has been evaluated in the symptomatic relief of osteoarthritis, the management of acute pain (including postoperative and dental pain) and the treatment of primary dysmenorrhea.[7] Rofecoxib is also currently being investigated for its potential in the treatment of rheumatoid arthritis and Alzheimer’s disease, although the latter indication is beyond the scope of this review. This review focuses on the use of rofecoxib in the management of osteoarthritis, acute pain and rheumatoid arthritis; the use of rofecoxib in the management of osteoarthritis and acute pain has been reviewed previously in Drugs by Scott and Lamb.[8]

2. Pharmacodynamic Properties

2.1 Inhibition of Cyclo-Oxygenase Isoforms

*In vitro* data show that rofecoxib is a selective and potent inhibitor of the COX-2 enzyme.[9,10]
Concentrations required to inhibit COX-2 activity by 50% (IC₅₀) were 0.018 to 0.046 μmol/L;[9,10] these values are markedly lower than the IC₅₀ value for COX-1 (>50 μmol/L).[10] Rofecoxib has an approximately 1000-fold greater selectivity for COX-2 than COX-1.[10] In contrast, the IC₅₀ values for COX-1 and COX-2 inhibition with the NSAID indomethacin were 0.018 and 0.027 μmol/L, respectively.[9]

Data derived from human whole blood COX-1 and COX-2 assays indicate that rofecoxib has the highest \textit{in vitro} selectivity ratio (COX-1 IC₅₀/COX-2 IC₅₀) for the inhibition of COX-2 compared with other commonly used NSAIDs such as celecoxib, meloxicam, diclofenac and indomethacin (35.5 vs 6.6, 2, 3 and 0.4, respectively).[10]

In healthy volunteers (n = 16), the mean IC₅₀ value for single doses of rofecoxib for lipopolysaccharide (LPS)-stimulated prostaglandin E₂ (PGE₂) production, an indicator of COX-2 activity, was 0.77 μmol/L, over a 25 to 1000mg dose range.[9] The IC₅₀ value for indomethacin 5 to 75mg (n = 9) for LPS-stimulated PGE₂ production was 0.3 μmol/L. There was no significant inhibition of thromboxane B₂ (TXB₂) generation, a measure of COX-1 activity, with rofecoxib at single doses of up to 1000mg; the IC₅₀ value for indomethacin was 0.09 μmol/L.[9] Similar results for both rofecoxib and indomethacin were obtained at steady-state in 8 healthy volunteers with doses >10-fold higher than those associated with efficacy in osteoarthritis.[11]

2.2 Anti-inflammatory, Antipyretic and Analgesic Effects

2.2.1 In Humans

In a randomised, double-blind study, rofecoxib has demonstrated antipyretic and analgesic effects in volunteers with fever caused by infection.[12]

In 94 patients with a 38 to 40 (mean 38.5) °C fever induced by either an upper respiratory tract infection or a suspected benign systemic viral infection, single-dose rofecoxib 12.5 or 25mg significantly decreased body temperature 1 to 1.5 hours after administration of the drug compared with placebo (p < 0.01). Rofecoxib 25mg achieved a significantly greater decrease in body temperature 5 and 6 hours after administration compared with rofecoxib 12.5mg (p < 0.05). In comparison with placebo a single dose of ibuprofen 400mg significantly decreased body temperature 30 minutes after administration (p < 0.01).[12] Rofecoxib 25mg and ibuprofen achieved a similar decrease in body temperature from 3.5 to 6 hours after administration compared with baseline (1.3 vs 1.2 °C at 6 hours). This study demonstrated that a naturally occurring fever can be reversed with a selective COX-2 inhibitor, suggesting COX-2 may have a primary role in the generation of fever.[12]

2.2.2 In Animal Models

In animal models of inflammation, pain and fever, rofecoxib demonstrated similar efficacy to the traditional NSAIDs indomethacin and diclofenac.[10,12]

Rofecoxib effectively inhibited oedema of the rat paw in response to injected carrageenan; the dose required to inhibit 50% (ID₅₀) of the oedema was 1.5 mg/kg which was comparable with indomethacin (ID₅₀ 2 mg/kg).[10] Likewise, hyperalgesia induced by injection of carrageenan 4.5mg into the rat paw was reversed dose-dependently by oral rofecoxib (ID₅₀ 1.0 mg/kg) or indomethacin (ID₅₀ 1.5 mg/kg).[10]

Endotoxin (LPS)-induced pyrexia in rats was reduced by administration of rofecoxib at the plateau of temperature elevation (5 hours; ID₅₀ 0.24 mg/kg). The potency of rofecoxib was approximately 5 times that of indomethacin (ID₅₀ 1.07 mg/
Similar results were obtained following LPS-induced pyrexia in squirrel monkeys; rofecoxib 3 mg/kg or diclofenac 3 mg/kg significantly (p < 0.05 vs vehicle controls) reversed pyrexia at 220 to 240 minutes after the LPS injection.[12]

2.3 Ulcerogenic Potential

Rofecoxib has less effect on the GI mucosa, and is therefore less likely to cause GI complications than aspirin, naproxen, ibuprofen or indomethacin.[13-16]

In a randomised, double-blind study, gastroduodenal ulceration after 7 days of treatment in 170 healthy volunteers was significantly lower in those receiving rofecoxib 250mg once daily than in those receiving either ibuprofen 800mg 3 times daily or aspirin 650mg 4 times daily (12% of volunteers with ≥1 or 2 gastric or duodenal erosions or an ulcer vs 71 and 94%, p < 0.001) [each study agent was taken with food].[13] Compared with rofecoxib, a slightly lower incidence of ulceration was noted in placebo recipients (8%).[13]

Gastric mucosal prostaglandin synthesis was evaluated in 24 healthy volunteers receiving either rofecoxib 50mg once daily then placebo (each for 5 days) or naproxen 500mg twice daily then placebo (each for 5 days) in a randomised, crossover trial.[16] Results from endoscopically-obtained antral biopsy samples demonstrated that, relative to placebo, rofecoxib increased the synthesis of PGE2 by 18% compared with a 65% decrease with naproxen. COX-2 dependent LPS-induced PGE2 production was inhibited by 80% for rofecoxib and 83% for naproxen, whereas serum TXB2 generation, a measure of COX-1 activity, was unaffected by rofecoxib and inhibited by 94% with naproxen.[16]

Intestinal permeability is 3-fold greater with indomethacin 50mg 3 times daily (p < 0.05 vs baseline) than with rofecoxib 25 or 50mg once daily or placebo.[14] In a double-blind, crossover study in 39 healthy volunteers, permeability was measured by urinary recovery of chromium-51 labelled ethylene diamine tetra-acetate (51CrEDTA) at the end of each 7-day treatment period. Urinary excretion ratios on day 7 relative to baseline were 0.82, 1.01 and 1.58 for rofecoxib 25mg, rofecoxib 50mg and indomethacin 150mg, respectively (p = 0.001 for indomethacin vs placebo).[14] The day 7 to baseline ratios for 5 hour urinary excretion of 51CrEDTA were greater for indomethacin than placebo and rofecoxib 12.5 or 25mg (p < 0.001).

Ibuprofen 800mg 3 times daily was associated with GI microbleeding resulting in a higher rate of faecal blood loss over a 28-day period than either rofecoxib 25 or 50 mg/day or placebo in 67 healthy volunteers enrolled in a randomised double-blind study.[15] At week 4 of treatment, approximately 2ml of faecal blood loss (assessed using 51Cr-labelled red blood cells) occurred per day with ibuprofen compared with approximately 1 ml per day with rofecoxib or placebo (p < 0.001).

2.4 Platelet Function

Rofecoxib had no significant effect on TXB2 production by calcium ionophore-challenged human platelets in vitro, suggesting little, or no, COX-1 inhibition. The rofecoxib IC50 value of >20 μmol/L was markedly higher than the IC50 values for indomethacin or diclofenac (0.002 to 0.004 μmol/L).[10]

In an ex vivo study involving 24 healthy volunteers, once-daily rofecoxib (50mg for 10 days) had no effect on either TXB2 inhibition or the antiplatelet activity of low dose aspirin (81mg once daily for 7 days).[17] The rofecoxib dosage used in this study was twice that recommended for the treatment of osteoarthritis (section 6). In 76 healthy female volunteers, platelet aggregation following 6 days of treatment with rofecoxib 12.5 or 25mg once daily was not significantly affected relative to placebo.[18] In contrast, diclofenac 50mg 3 times daily, ibuprofen 800mg 3 times daily and naproxen sodium 550mg twice daily significantly inhibited platelet aggregation, by a mean of approximately 25, 78 and 90%, respectively, compared with placebo (p < 0.001). Bleeding times after rofecoxib or diclofenac treatment were not significantly different compared with baseline; however, relative to baseline, both ibuprofen and naproxen significantly prolonged bleeding times by 1.57 and 2.41 minutes, respectively (p < 0.002).[18]
3. Pharmacokinetic Properties

The pharmacokinetic parameters of single and multiple doses of rofecoxib have been evaluated in healthy volunteers. The data presented in this section are based on the prescribing information,[19] information from the American Society of Health System Pharmacists (AHFS)[20] and Mosby’s GenRx.[21] The pharmacokinetic parameters of multiple doses of rofecoxib 12.5 and 25mg are presented in table I.

Rofecoxib is well absorbed after oral administration; mean maximum plasma concentrations (Cmax) were reached approximately 2 to 3 hours after administration (table 1) [with an individual variability of 2 to 9 hours]. However, this may not reflect the true rate of absorption, as Cmax may occur as a secondary peak in some individuals.[20,21] The cause of secondary peaks, mostly occurring at higher doses, is unknown; however, it has been estimated that it is not the result of enterohepatic recycling.[22] After single doses of rofecoxib 25mg, Cmax was 207 μg/L and the area under the plasma concentration-time curve (AUC) was 3286 μg/ L • h.[21] The mean oral bioavailability after therapeutically recommended single doses of rofecoxib (12.5, 25 or 50mg) was 93%.[20,21]

Following administration of multiple doses of rofecoxib (25 mg/day), a steady-state mean Cmax of 321 μg/L was reached within 4 days (table I). Drug accumulation has been observed in individuals receiving rofecoxib; the accumulation factor was reported to be 1.67.[20,21] Administration of rofecoxib with a high fat meal does not significantly affect Cmax or the extent of absorption. However, time to reach Cmax is delayed by 1 to 2 hours.[20,21]

At drug concentrations of 0.05 to 25 mg/L, rofecoxib is approximately 87% bound to plasma proteins. Distribution of rofecoxib into various human tissues has not been fully characterised.[20]

Radioactively labelled rofecoxib is extensively metabolised in the liver, primarily via reduction by cytosolic enzymes. The 2 main inactive metabolic products are the cis-dihydro and trans-dihydro derivatives which account for approximately 56% of the recovered radioactivity in urine.[20,21] A small percentage (approximately 9%) of the administered dose is recovered as the glucuronide of the hydroxy derivative, a product of oxidative metabolism. Cytochrome P450 plays a minor role in the metabolism of rofecoxib.

Rofecoxib is eliminated via hepatic metabolism with <1% of the administered dose excreted unchanged in the urine. Approximately 72% of a single radiolabelled 125mg dose is excreted into the urine as metabolites, and 14% is excreted unchanged in the faeces.[20,21]

3.1 Special Populations

3.1.1 Elderly Patients

Oral administration of rofecoxib 25mg to adults ≥65 years of age resulted in a 34% increase in AUC compared with younger adults.[20] While dosage adjustment in these patients is not necessary, treatment should be initiated at the lowest possible dose (see section 7).[21] When rofecoxib was administered to elderly patients with either calcium carbonate antacid or magnesium/aluminium antacid, there were 13 and 8% decreases, respectively, in the absorption of rofecoxib.[21] Cmax is decreased by approximately 20% when rofecoxib is given with either antacid.[21]

3.1.2 Patients with Renal or Hepatic Impairment

Data on the pharmacokinetic parameters of rofecoxib in individuals with renal or hepatic impairment are limited.

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**Table I. Pharmacokinetic parameters of multiple doses of orally administered rofecoxib 12.5 or 25mg once daily at steady state[20-22]**

<table>
<thead>
<tr>
<th></th>
<th>12.5mg</th>
<th>25mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (μg/L)</td>
<td>NR</td>
<td>321</td>
</tr>
<tr>
<td>AUC (μg/L • h)</td>
<td>NR</td>
<td>4018</td>
</tr>
<tr>
<td>tmax (h)</td>
<td>2-3a</td>
<td>2-3a</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>=17</td>
<td>=17</td>
</tr>
<tr>
<td>Vd (L)</td>
<td>91</td>
<td>86</td>
</tr>
<tr>
<td>CL (L/h)</td>
<td>8.5</td>
<td>7.2</td>
</tr>
</tbody>
</table>

*After a single dose. AUC = area under the plasma concentration-time curve; CL = clearance rate; Cmax = maximum plasma concentration; NR = not reported; t1/2 = elimination half life; tmax = time to reach Cmax; Vd = volume of distribution.*
There were no significant differences in the AUC of rofecoxib between patients with mild hepatic impairment (Child-Pugh score ≤ 6) and healthy volunteers with normal hepatic function.\textsuperscript{[20,23]} However, AUC was increased by 69% in 4 patients with moderate hepatic impairment (Child-Pugh score 7-9) compared with 4 healthy volunteers.\textsuperscript{[20,23]} More data are needed to fully evaluate the pharmacokinetics of rofecoxib in patients with moderate hepatic impairment; there are currently no available data for patients with severe hepatic impairment.\textsuperscript{[20]}

C\textsubscript{max} and AUC values were decreased by 18 and 9% in 6 individuals with end-stage renal failure undergoing dialysis 4 hours after receiving rofecoxib.\textsuperscript{[21]} There are no pharmacokinetic data available on the effects of rofecoxib in advanced renal disease, therefore rofecoxib is not recommended in these patients.

### 3.2 Drug Interactions

Data in this section are derived from the prescribing information,\textsuperscript{[19]} AHFS\textsuperscript{[20]} and from papers\textsuperscript{[24]} the majority of which are published as abstracts\textsuperscript{[25-27]} (see also table VI).

In 21 patients with rheumatoid arthritis, the addition of rofecoxib (12.5, 25 or 50 mg/day for 21 days) to a stable oral methotrexate regimen (7.5 to 20 mg/week) had no clinically significant effect on plasma methotrexate concentrations.\textsuperscript{[27]} However, when rofecoxib was administered at a dosage of 75 mg/day for 10 days, in combination with methotrexate 7.5 to 15 mg/week, there was a mean 23% increase in rofecoxib plasma concentrations and an equivalent decrease in methotrexate renal clearance.\textsuperscript{[27]} Standard monitoring of methotrexate-related toxicity should be continued if rofecoxib and methotrexate are coadministered (see table VI).

In 12 healthy volunteers, rofecoxib at a dosage of 250mg once daily for 14 days had no clinically significant effect on the plasma concentrations of either oral prednisone 30mg or intravenous prednisolone 30mg, both administered on days 10 and 14.\textsuperscript{[26]}

Serum concentrations and urinary excretion of a single dose of digoxin 0.5mg were unaffected by once-daily administration of rofecoxib 75mg for 11 days in 10 healthy volunteers.\textsuperscript{[24]} Serum concentrations of ethinylestradiol and norethindrone in 18 healthy women were not significantly affected by daily administration of rofecoxib at doses as high as 175mg.\textsuperscript{[25]}

Rifampicin is a potent inducer of hepatic metabolism. In patients receiving rofecoxib and potent inducers of hepatic metabolism a starting dosage of 25 mg/day should be considered (see table VI). Patients receiving rofecoxib with either warfarin or rifampicin should be monitored for potential interactions.\textsuperscript{[20]} A 50% decrease in the plasma concentration of rofecoxib occurred upon concomitant administration with rifampicin (rifampin) 600mg/day.\textsuperscript{[20]} There are no clinically significant pharmacokinetic interactions between rofecoxib and ketoconazole or cimetidine.

### 4. Therapeutic Efficacy

Rofecoxib has been evaluated in clinical trials in 3 distinct indications:
- osteoarthritis
- acute pain
- rheumatoid arthritis.

Within the context of acute pain, the efficacy of rofecoxib has been evaluated in patients with dental pain, postoperative pain and primary dysmenorrhea. Each indication is discussed in detail in the following sections.

#### 4.1 Osteoarthritis

In the treatment of patients with osteoarthritis, rofecoxib, administered once daily, has been compared with placebo,\textsuperscript{[28-31]} celecoxib,\textsuperscript{[32]} paracetamol (acetaminophen),\textsuperscript{[32]} diclofenac,\textsuperscript{[31,33,34]} ibuprofen,\textsuperscript{[29-31]} naproxen\textsuperscript{[35]} and nabumeton\textsuperscript{[36]} in trials of 1 to 52 weeks’ duration. Five studies are fully published,\textsuperscript{[28,30,31,33,36]} the remainder are abstracts. The majority of studies were randomised and double-blind; 2 studies were randomised but did not state blinding.\textsuperscript{[29,34]} These trials included only patients with osteoarthritis of the knee or hip.
The 5 fully published trials reported their inclusion criteria in detail. Patients were required to be ≥40 years of age, or >80 years of age in 1 study,\(^{[36]}\) with osteoarthritis of the knee or hip for ≥6 months’ duration prior to trial entry.\(^{[28,30,31,33,36]}\)

Osteoarthritis was diagnosed on the basis of clinical and radiographic evidence and had to meet the following criteria:

- radiographic evidence of joint space narrowing and osteophytes for the knee and joint space narrowing for the hip
- knee or hip the primary site of pain and/or disability
- American Rheumatism Association functional class I, II or III
- history of benefit from regularly taking NSAIDs.\(^{[28]}\)

Three studies evaluated patients according to prior NSAID or paracetamol use.\(^{[30,31,33]}\) After discontinuation of NSAID therapy, patients were included in the trials if they reported at least moderate pain when walking [40mm on the visual analogue scale (VAS)] and a minimum increase in pain of 15mm (VAS) when walking, compared with initial screening levels.\(^{[30,33]}\) In addition, the physician’s disease assessment had to have worsened. For those previously taking paracetamol (not allowed within 12 hours of assessments), inclusion was allowed if they reported moderate pain upon walking and both patients and physicians assessed the disease status to be fair, poor or very poor.\(^{[30,33]}\) Patients enrolled in 1 study simply had to demonstrate a worsening in the signs and symptoms of osteoarthritis after a washout period for prior NSAID use.\(^{[31]}\) Those with previous paracetamol use had to consistently demonstrate at least moderate symptoms of osteoarthritis.\(^{[31]}\)

One study (reported as an abstract) specifically included only patients who were taking paracetamol (1.2 to 4 g/day) prior to randomisation to either rofecoxib, ibuprofen or placebo.\(^{[29]}\)

The primary end-points varied across the trials. Pain upon walking, assessed using the VAS 100mm [question 1 of the Western Ontario McMaster Universities Osteoarthritis Index (WOMAC)], and/or patient global assessment of response to therapy (PGART) \([0 = \text{none to } 4 = \text{excellent}]\) were the primary end-points in 6 trials.\(^{[29-33,35]}\)

Four of these trials also included a physician assessment of disease status \([0 = \text{very poor to } 4 = \text{very well}].\(^{[29-31,33]}\)

One trial also assessed pain at night and at rest, and morning stiffness.\(^{[32]}\)

Patient global assessment of disease status using the VAS \((0 \text{mm} = \text{very well to } 100 \text{mm} = \text{very poor})\) was the primary end-point in 1 trial.\(^{[36]}\)

The remaining trial used the WOMAC pain subscale and a patient assessment of arthritic pain \((100 \text{mm VAS}).\(^{[28]}\)

One study assessed joint space narrowing, which reflects disease progression, using semi-flexed posterior-anterior radiographs at baseline and at 1 year.\(^{[34]}\)

The results from trials with similar primary end-points and for which there are data available, including 5 fully published trials,\(^{[28,30,31,33,36]}\) are presented in table II.

### 4.1.1 Placebo Comparison

There is only 1 fully reported study comparing rofecoxib 25 and 125 mg/day with placebo in patients with osteoarthritis of the knee \((n = 262).\(^{[28]}\)

Compared with placebo, rofecoxib recipients showed significant improvements in the primary end-points, the WOMAC pain subscale and patient assessment of arthritic pain after 1 and 2 weeks of treatment, respectively \((p < 0.001 \text{ for both dosages})\); these differences remained significant at 6 weeks \((\text{table II, } p < 0.001 \text{ for both dosages}).\)

Rofecoxib recipients also fared significantly better for the secondary end-points, WOMAC physical function \((=46 vs 11\% \text{ improvement from baseline for placebo})\) and stiffness subscales \((47 \text{ to } 50 \text{ vs } 11\% \text{ for placebo})\), and patient and investigator global assessment of disease status \((\text{table II for the latter})\) and response to therapy \((46 \text{ to } 57\% \text{ vs } 11 \text{ to } 19\% \text{ for placebo, } p < 0.001).\(^{[28]}\)

There were no significant differences between the different dosages of rofecoxib for any end-point. Of those receiving placebo, 43% withdrew from treatment, the majority because of lack of efficacy \((29\%)\), compared with 12 and 23% with rofecoxib 25 and 125mg, respectively \((p < 0.05).\)
Table II. Results of trials comparing rofecoxib (R) with placebo (PL) and various NSAIDs in patients with osteoarthritis of the hip or knee

<table>
<thead>
<tr>
<th>Reference (trial design details)</th>
<th>No. of patients evaluated</th>
<th>Trial duration (wk)</th>
<th>Dosage</th>
<th>Improvement from baseline (%) change</th>
<th>PGART&lt;sup&gt;b&lt;/sup&gt; (mean score)</th>
<th>WOMAC pain subscale&lt;sup&gt;c&lt;/sup&gt; (mean change from baseline)</th>
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<tr>
<td><strong>Placebo-controlled trial</strong></td>
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<tr>
<td>Ehrich et al.&lt;sup&gt;[28]&lt;/sup&gt;</td>
<td>262</td>
<td>6</td>
<td>R 25mg od</td>
<td>54&lt;sup&gt;***&lt;/sup&gt;</td>
<td>–36&lt;sup&gt;***d&lt;/sup&gt;</td>
<td>–28.1***</td>
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<td></td>
<td></td>
<td></td>
<td>R 125mg od</td>
<td>57&lt;sup&gt;***&lt;/sup&gt;</td>
<td>–38&lt;sup&gt;***d&lt;/sup&gt;</td>
<td>–28***</td>
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<td></td>
<td></td>
<td></td>
<td>PL</td>
<td>19</td>
<td>−15.4&lt;sup&gt;d&lt;/sup&gt;</td>
<td>−7.1</td>
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<tr>
<td><strong>Active comparators</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Cannon et al.&lt;sup&gt;[33]&lt;/sup&gt;</td>
<td>784</td>
<td>52</td>
<td>R 12.5mg od</td>
<td>47&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.3&lt;sup&gt;a&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
<td>R 25mg od</td>
<td>46&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>−27.3</td>
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<td></td>
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<td>I 800mg tid</td>
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<td></td>
<td>PL</td>
<td>NR</td>
<td>1.9</td>
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<tr>
<td>Daniels et al.&lt;sup&gt;<a href="f">29</a>&lt;/sup&gt;</td>
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<td>−23.4**</td>
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<td>−24.8**</td>
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<td>−26</td>
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<td>PL</td>
<td>NR</td>
<td>NR</td>
<td>−5</td>
</tr>
</tbody>
</table>

<sup>a</sup> This end-point refers to global assessment of disease status.<sup>[28,30,33]</sup>

<sup>b</sup> Response to therapy ranged from 0 = none to 4 = excellent.<sup>[29,30,33]</sup>

<sup>c</sup> Pain scale ranged from 0 = no pain to 100 = extreme pain.

<sup>d</sup> The end-point was patient assessment of arthritic pain measured as a mean improvement from baseline (100mm VAS scale; 0mm = no pain to 100mm = extreme pain).

<sup>e</sup> 26-week data estimated from a figure.

<sup>f</sup> Abstract.

<sup>g</sup> Values estimated from a figure.

**bid** = twice daily; **db** = double-blind; **I** = ibuprofen; **mc** = multicentre; **NA** = nabumetone; **N** = naproxen; **NR** = not reported; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **od** = once daily; **PGART** = Patient Global Assessment of Response to Therapy; **r** = randomised; **tid** = three times daily; **VAS** = visual analogue scale; **WOMAC** = Western Ontario McMasters Universities Osteoarthritis Index; *p ≤ 0.05 vs PL; **p < 0.01 vs PL; ***p < 0.001 vs PL; †p < 0.005 vs I.
Rofecoxib 12.5 or 25 mg/day was also significantly better than placebo, in comparative trials with ibuprofen, with respect to pain upon walking,[30] physician assessment of global disease status,[30,31] PGART[30,31] and the WOMAC pain subscale (table II).[30,31]

4.1.2 Active Comparisons

In randomised double-blind trials, rofecoxib 12.5 or 25 mg/day had significantly better efficacy than celecoxib 200 mg/day or paracetamol 4 g/day[32] and was similar in efficacy to ibuprofen 2400 mg/day[29,31] (although rofecoxib was slightly more efficacious in 1 study[30]), diclofenac 150 mg/day,[33,34] nabumetone 1500 mg/day[36] and naproxen 1000 mg/day[35] in patients with osteoarthritis. However, in 1 study diclofenac 150 mg/day was generally more efficacious than rofecoxib 12.5 or 25 mg/day.[31]

Comparisons with Celecoxib

In comparison with celecoxib 200 mg/day, rofecoxib 25 mg/day was significantly better at relieving night pain on days 2 and 3 and rest pain on days 2 to 6 in 379 patients (p < 0.05, specific data not reported) in a 6-week randomised, double-blind trial (reported as an abstract).[32] Rofecoxib was also significantly more effective than celecoxib for relieving pain when walking on days 2 to 4 (p < 0.05).[32] A slightly higher proportion of celecoxib recipients (9.3%) discontinued the trial early because of lack of efficacy compared with 7.4% recipients of rofecoxib 12.5 mg/day and 8.5% recipients of rofecoxib 25 mg/day.

Comparisons with Traditional NSAIDs

There were no significant differences with regard to pain upon walking between rofecoxib and ibuprofen or diclofenac (table II).[30,33] Likewise, improvements in the physician global assessment of disease status,[33] the patient assessment of response to therapy and the WOMAC pain subscale scores were similar between rofecoxib and diclofenac,[31,33] although mean scores for diclofenac were numerically higher for the 2 latter scales (table II).[31,33] For the 2 former measures, rofecoxib 25 mg was significantly more effective than ibuprofen in 1 study[30] and patient assessment of response to therapy scores showed slightly greater improvement with rofecoxib 25 mg in 2 studies (significance levels not reported) [table II].[29,31]

Rofecoxib 12.5 or 25 mg and ibuprofen 2400 mg showed similar efficacy in improving the physician global assessment of disease status (–1.3, –1.5 and –1.3, respectively) and pain upon walking (–29.3, –35.2 and –31.8, respectively) in a 6-week study.[31] In this study, rofecoxib 12.5 and 25 mg were also compared with diclofenac 150 mg for 1 year; diclofenac showed a significantly greater improvement than either dose of rofecoxib for the physician global assessment of disease status (–1.6, –1.5 and –1.5, respectively) [p < 0.05], and patient global assessment of disease status (–30, –26.2 and –25.1, respectively) [p = 0.01].[31]

For other measures of efficacy, such as the physical function and stiffness WOMAC subscales and study joint tenderness, improvement from baseline was slightly but not significantly higher for rofecoxib 12.5 or 25 mg/day than for ibuprofen 2400 mg/day;[30,31] diclofenac 150 mg/day was at least as effective as rofecoxib.[31,33]

Prior paracetamol or NSAID use did not have a significant effect on treatment outcome.[30,33] Rofecoxib 12.5 and 25 mg/day and nabumetone 1500 mg/day were compared with placebo in 341 patients with osteoarthritis (aged ≥80 years).[36] Mean changes from baseline in the patient global assessment of disease status measured using the VAS were significantly greater with both rofecoxib (=25 mm for both dosages) and nabumetone (26 mm) than with placebo (15 mm) [p < 0.001].[36]

Results from a comparative trial of rofecoxib 12.5 mg and naproxen 500 mg twice daily showed no differences in improvements from baseline in pain upon walking (86 vs 85%, respectively). However, these results must be interpreted with caution as the 1-week duration of this trial is not long enough to accurately reflect an improvement in patients with osteoarthritis.[35]

Two 1-year trials (reported in abstract form) evaluated the effect of rofecoxib 12.5 or 25 mg/day, and diclofenac 50 mg 3 times daily on joint...
Joint space width decreases were noted with all 3 treatment groups (0.14, 0.27 and 0.18 mm, respectively); there were no significant differences between rofecoxib and diclofenac treatment groups.

**Comparison with Paracetamol**

In terms of rest pain, treatment with rofecoxib 25 mg/day produced a greater clinical response than paracetamol 1000 mg/day after day 2 in 379 patients (p < 0.01, specific data not reported) in a 6-week randomised, double-blind trial (reported as an abstract). Rofecoxib 12.5 mg was significantly better than paracetamol for relieving rest pain on days 4 to 5 (p < 0.01). Pain upon walking was significantly improved for the first 5 days of therapy with rofecoxib 25 mg (p < 0.001), and for days 3 to 6 with rofecoxib 12.5 mg (p < 0.05) compared with paracetamol. 18% of paracetamol recipients discontinued the trial early because of a lack of efficacy compared with 7.4% and 8.5% of rofecoxib, 12.5 and 25 mg/day recipients.

**4.2 Acute Pain**

**4.2.1. Postsurgical Dental Pain**

For the treatment of postsurgical dental pain, single dose rofecoxib has been compared with single doses of celecoxib, naproxen sodium and ibuprofen in double-blind, randomised, placebo-controlled trials.

Three studies were fully published (table III), the remainder are reported as abstracts. In general, inclusion criteria required participants to be ≥ 18 years of age, have ≥2 third molars removed, ≥1 of which was impacted, and have experienced either moderate or severe pain after dental surgery and be otherwise healthy.

Total pain relief at 8 hours (6 hours in 1 study) determined by summing the time-weighted scores for pain relief (TOPAR8) [0 = none to 4 = complete], was the primary end-point in all trials. Secondary end-points included time to perceptible pain relief (a stopwatch was used to determine the time from when the study drug was administered to the times when perceptible and meaningful pain relief was achieved), maximum pain relief during the first 8 hours postdose, time to rescue medication and global evaluation of study drug efficacy at 8 and 24 hours.

After receiving the study medication patients in 2 trials were encouraged to wait ≥ 90 minutes before taking any rescue medication.

**Results**

In patients with postsurgical dental pain, rofecoxib 50 to 500 mg was significantly better in providing total pain relief at 6 to 8 hours than either placebo (p < 0.01) or celecoxib 200 mg (p < 0.001) and was generally similar in efficacy to naproxen sodium 550 mg and ibuprofen 400 mg. Rofecoxib 12.5 or 25 mg was also significantly better than placebo (p < 0.01). The results for the fully published studies are presented in table III.

Rofecoxib had a more rapid analgesic effect than celecoxib (approximately 30 minutes vs 1 hour; p < 0.05) and was similar in this respect to ibuprofen, as expected, placebo recipients generally did not experience any appreciable pain relief. Furthermore, the duration of analgesic effect was prolonged with rofecoxib compared with celecoxib, ibuprofen or placebo as evidenced by significantly greater mean pain relief scores at 24 hours (table III). In addition, fewer rofecoxib recipients required rescue medication within 24 hours of administration (table III). In 1 trial, median time to the use of rescue medication was > 24 hours for rofecoxib, 5 to 9 hours for celecoxib and ibuprofen, and 1.5 hours for placebo.

Patient global evaluation of efficacy at 6 and 8 hours favoured rofecoxib, reaching significance compared with celecoxib and placebo (p < 0.01) [table III].

It is important to note that daily doses of celecoxib 100 to 400 mg have been used in clinical trials of postoperative pain management. Therefore, the single 200 mg dose used in the comparative trial with rofecoxib may have been subtherapeutic.

Overall, with respect to TOPAR8 scores, rofecoxib 25 to 50 mg was significantly more effective than rofecoxib 12.5 mg (p ≤ 0.006) and 50 mg was more effective than 25 mg, in 331 patients, although the difference was not statistically signifi-
There were no significant differences between the 50 and 500mg doses of rofecoxib (table III).

### 4.2.2 Postoperative Surgical Pain

Rofecoxib has been evaluated for its efficacy as postoperative pain relief in 3 randomised, double-blind, placebo-controlled trials in patients undergoing orthopaedic surgery (compared with naproxen sodium),\(^\text{42}\) spinal fusion surgery (compared with celecoxib)\(^\text{43}\) or radical prostatectomy.\(^\text{44}\)

Two trials have been fully published,\(^\text{42,43}\) and 1 is available as an abstract.\(^\text{44}\) Inclusion criteria generally included patients aged ≥18 years,\(^\text{42,43}\) who weighed >40kg\(^\text{43}\) and who did not have any significant illness such as renal insufficiency, history of peptic ulcer, uncontrolled hypertension or inherited bleeding disorder.\(^\text{42,43}\) In 1 trial, patients had to have moderate to severe pain following discontinuation of immediate postoperative analgesia.\(^\text{42}\)

Primary end-points in 2 trials were pain scores measured using either the VAS\(^\text{44}\) or a verbal analogue pain scale (VbAS)\(^\text{43}\) both scales ranged from 0 = no pain to 10 = worst pain imaginable. Additional pain assessments and morphine use were also evaluated by a blinded observer in 1 trial\(^\text{43}\) and by the patients themselves (overall pain relief 0 = poor to 4 = excellent), amount of rescue medication (morphine) if needed and time to perceptible and peak pain relief up to 12 hours postdose on day 1.\(^\text{42}\)

#### Results

The efficacy of rofecoxib in relieving postoperative pain appears, on the basis of preliminary results, to be related to the specific indication being treated. Rofecoxib was significantly more effec-

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### Table III. Fully published double-blind, randomised, single-dose studies comparing the clinical efficacy of rofecoxib (R) with that of celecoxib (C), ibuprofen (I) or placebo (PL) in the treatment of postsurgical dental pain

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Dose (mg)</th>
<th>TOPAR(^a) (0-32 scale)</th>
<th>Time to perceptible pain relief (h)</th>
<th>Rescue medication within 24 hours (% of patients)</th>
<th>Patient global evaluation of study drug at 8 hours(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ehrich et al.(^9)</td>
<td>104</td>
<td>R 50</td>
<td>14.1**</td>
<td>1.5**</td>
<td>&lt;25(^f)</td>
<td>2.3**(e)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R 500</td>
<td>16**</td>
<td>1.2**</td>
<td>&lt;25(^f)</td>
<td>2.9**(e)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I 400</td>
<td>15.2**</td>
<td>1.2**</td>
<td>&lt;25(^d)</td>
<td>2.6**(e)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL</td>
<td>3.2</td>
<td>4.5(^c)</td>
<td>75(^d)</td>
<td>0.5(^e)</td>
</tr>
<tr>
<td>Malmstrom et al.(^40)</td>
<td>272</td>
<td>R 50</td>
<td>18.3**(^t)</td>
<td>0.5**(^t)</td>
<td>49**(^tt)</td>
<td>2.3**(^t)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C 200</td>
<td>12.5**</td>
<td>1**</td>
<td>78</td>
<td>1.6**</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I 400</td>
<td>17**(^t)</td>
<td>0.4**(^t)</td>
<td>76</td>
<td>2.2**(^t)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL</td>
<td>4</td>
<td>&gt;4</td>
<td>91</td>
<td>0.5</td>
</tr>
<tr>
<td>Morrison et al.(^39)</td>
<td>151</td>
<td>R 50</td>
<td>13.8*</td>
<td>0.7(^f)</td>
<td>56(^t)</td>
<td>2.0*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>I 400</td>
<td>11.8*</td>
<td>0.8(^f)</td>
<td>82</td>
<td>1.8*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PL</td>
<td>5.4</td>
<td>NE(^f)</td>
<td>92</td>
<td>0.8</td>
</tr>
</tbody>
</table>

\(\text{TOPAR}^a\): Total pain relief calculated as the summed, time-weighted pain relief scores (0 = none to 4 = complete) to 8 hours\(^39,40\) or 6\(^9\) hours. 

\(\text{b}^\text{Scale 0 = poor to 4 = excellent.}\)

\(\text{c}^\text{Time to meaningful pain relief.}\)

\(\text{d}^\text{Proportion of R and I recipients needing rescue medication at the end of the 6-hour study period. Proportion of PL recipients who required rescue medication within 2 hours of receiving the dose.}\)

\(\text{e}^\text{Data (estimated from a graph) are for global evaluation at 6 hours.}\)

\(\text{f}^\text{Time to confirmed perceptible pain relief in 50% of patients.}\)

NE = not estimable; *p < 0.05; **p < 0.001 vs PL; †p < 0.001 vs C; ‡p < 0.05 vs I.
tive than celecoxib in treating patients who had spinal fusion surgery, and was better than placebo and similar to naproxen sodium in relieving orthopaedic surgical pain. However, rofecoxib was similar to placebo in treating postoperative pain after radical prostatectomy.

Rofecoxib 50mg (1 hour prior to anaesthetic induction) was significantly more effective than either celecoxib 200mg (1 hour prior to anaesthetic induction) or placebo in relieving postoperative pain in 60 patients who had decompressive lumbar laminectomy with spinal fusion. Postoperative mean VbAS scores for rofecoxib recipients were significantly lower at 8, 12 and 16 hours postoperatively compared with placebo recipients and at 12 and 16 hours compared with those receiving celecoxib (p < 0.03) [fig. 2]. There were no significant differences between treatment groups after 20 hours, although rofecoxib mean VbAS scores remained the lowest at this time point (fig. 2). The total postoperative dose of supplemental morphine was also significantly less with rofecoxib than either placebo or celecoxib (71 vs 117 and 107mg, respectively, p < 0.0001). In addition, after 8 hours rofecoxib recipients required less morphine at each 4-hourly interval than patients receiving either placebo or celecoxib (mean dose 11.4 vs 18.8 and 18.6mg, respectively, p < 0.0001). Once again it is important to note that a subtherapeutic dose of celecoxib may have been used in this study (see section 4.2.1).

In 218 patients who underwent orthopaedic surgery (total hip or knee replacement or fracture repair), rofecoxib 50mg was superior to placebo and similar to naproxen sodium 550mg in providing postoperative analgesia on day 1. Over the 8 hour post-dose period the TOPAR8 scores were significantly higher with rofecoxib and naproxen sodium than with placebo (least squares mean 11.7 and 12.3 vs 5.8, p < 0.05). The onset of perceptible pain relief (in 50% of patients) was significantly quicker with rofecoxib than naproxen sodium (0.9 vs 1.2 hours, p < 0.05), and less supplemental morphine was required than with either naproxen sodium or placebo (1.5 tablets vs 1.8 and 2.2 respectively, p < 0.05 vs placebo). However, the patient’s global evaluation of efficacy at 8 hours was similar for both rofecoxib and naproxen sodium (1.8 and 1.7 vs 1 for placebo, p < 0.05). Data were also provided for days 2 to 5 of this study; however, naproxen sodium recipients received placebo over this time period and some rofecoxib recipients had a dose reduction to 25mg. Because there was no washout period, these results may be affected by a carryover effect and are, therefore, not discussed further.

A small study compared postoperative rofecoxib 50mg (1 hour before induction of anaesthesia) and placebo in 22 patients after radical prostatectomy. Between 1 and 24 postoperative hours there were no significant differences in VAS pain scores or supplemental morphine consumption between the 2 groups (specific data not reported). Furthermore, patients’ assessment of overall pain relief at 24 hours did not differ between rofecoxib and placebo recipients.

Fig. 2. Mean pain scores up to 24 hours after spinal fusion surgery in 60 patients receiving either rofecoxib 50mg, celecoxib 200mg or placebo, all administered 1 hour prior to anaesthetic induction. Pain was quantified on a verbal analogue pain scale where 0 represents no pain and 10 represents the worst pain imaginable. * p < 0.03 vs placebo at 8, 12 and 16 hours and celecoxib at 12 and 16 hours.
4.2.3 Primary Dysmenorrhoea

As a treatment for primary dysmenorrhoea, rofecoxib has been compared with naproxen sodium in 2 comparative, randomised, double-blind, placebo-controlled, crossover trials.[45,46] One study published its methodology in detail;[46] the other is reported in abstract form.[45] Inclusion criteria included women with moderate to severe primary dysmenorrhoea aged ≥18 years, who had negative serum β-human chorionic gonadotrophin, a gynaecological examination within the past year, no evidence of other causes of dysmenorrhoea and were otherwise healthy.[46] Nursing mothers, women abusing drugs or alcohol and women taking tricyclic antidepressants, analgesics, tranquillisers, hypnotics, sedatives or corticosteroids were excluded.

In both trials, rofecoxib was administered as a 50mg initial dose followed by a maintenance dose of 25mg daily as needed and naproxen sodium was administered as a 550mg initial dose followed by 550mg every 12 hours as needed.[45,46] In 1 trial, rofecoxib was also initially administered as a 25mg dose followed by a 25mg maintenance dose.[46]

The primary end-point in both trials was TOPAR8 (0 = none to 4 = complete).[45,46] Pain intensity (0 = none to 3 = severe), patients’ overall evaluation of the study drug at 8 and 72 hours (0 = poor to 4 = excellent) and need for additional doses of either the study drug or rescue medication were also end-points in 1 trial.[46]

Results
Rofecoxib 25 or 50mg, or naproxen sodium were significantly better than placebo in providing total pain relief up to 8 hours after the onset of moderate to severe pain (p ≤ 0.006).[45,46] In 127 patients, mean total pain relief scores were similar for both doses of rofecoxib and naproxen sodium (17.4, 18 and 18.4, respectively); all were significantly better than placebo (12.5, p ≤ 0.006).[46] Rofecoxib at an initial dose of 50mg was similar in efficacy to naproxen sodium in the patient’s overall evaluation of the study drug (mean 2.0 vs 1.9 for naproxen sodium); however, rofecoxib was favoured when compared with placebo (1.2, p ≤ 0.006).[46] Time to pain intensity difference from baseline was significantly less for naproxen sodium (1 hour) than either rofecoxib or placebo (1.5 hours, p ≤ 0.006).[46] As expected, a greater proportion of placebo recipients required rescue medication (45%) within 12 hours of pain onset [or took additional doses of study medication (24%)] than either rofecoxib (approximately 27% for both doses) or naproxen sodium (approximately 30%) [p ≤ 0.006].[46]

Similar findings were recorded in 63 patients with primary dysmenorrhoea.[45] Rofecoxib was significantly more effective than placebo and similar in efficacy to naproxen sodium in terms of overall evaluation of study drugs and remedication (p < 0.009). For rofecoxib, time to pain intensity difference from baseline was marginally less than for placebo and similar to naproxen.

4.3 Rheumatoid Arthritis

Two 1-year randomised, double-blind, trials have evaluated the efficacy of rofecoxib 5, 25 or 50mg compared with placebo[47,48] or rofecoxib 50mg compared with naproxen 500mg twice daily [VIGOR (VIOXX in GI Outcomes Research) study][49] in the treatment of over 8700 patients with rheumatoid arthritis. The VIGOR study was primarily designed to evaluate the GI tolerability of rofecoxib; however, secondary efficacy endpoints were also evaluated.

In 1 study, inclusion criteria specified patients must be aged ≥18 years with rheumatoid arthritis diagnosed after age 16 and at least 6 months prior to study entry and meeting the 1987 American College of Rheumatology (ACR) criteria. Patients must also have been taking therapeutically beneficial doses of NSAIDs for ≥25 of the 30 days before study entry (discontinued with a washout period).[47] Patients aged at least 50 years (or at least 40 years of age and receiving long term glucocorticoid therapy) were included in the second trial.[49]

Patients with systemic lupus erythematosus, spondyloarthopathy, polymyalgia rheumatica, gout, Paget’s disease, active GI bleeding or uncontrolled diabetes were excluded.[47] Exclusion cri-
Criteria for the VIGOR study included patients with a history of another type of inflammatory arthritis, inflammatory bowel disease, upper GI surgery, creatinine clearance of approximately ≤30 ml/min-ute, an unstable medical condition, a history of cancer, a history of cerebrovascular events in the 2 years prior to the study, alcohol or drug abuse in the 5 years prior to the study or a history of myocardial infarction or coronary bypass in the year preceding the study.[49]

Patient and investigator global assessment of disease activity (0 = very well to 4 = very poor) were the primary efficacy outcome measures [the primary end-point was confirmed GI events (see section 5.1)] in the VIGOR study.[49] A subset of patients also completed the Modified Health Assessment Questionnaire (MHAQ), evaluating functional disability, using a 4-point scale (0 = no difficulty to 3 = inability to perform a task).

In the other study, patients were randomised to receive rofecoxib 5, 25 or 50mg or placebo for 8 weeks;[47] at the end of 8 weeks, patients taking rofecoxib 25 or 50mg continued for an additional 44 weeks, whereas patients taking rofecoxib 5mg or placebo were reassigned to double-blind treatment with rofecoxib 25 or 50mg or naproxen 500mg 3 times daily for 44 days (reported as an abstract).[48]

4.3.1 Results
In 8076 patients with rheumatoid arthritis, once daily rofecoxib 50mg and naproxen 500mg twice daily had similar efficacy after a median follow-up of 9 months (table IV).[49] Improvement in global disease activity scores as assessed by the patient were 26 vs 27% for rofecoxib and naproxen, respectively; improvements in the investigator assessment of disease activity were 26 vs 28%, respec-

The primary end-point for the first 8 weeks was the number of patients that met the criteria for an ACR 20 response.[47] An ACR 20 response is defined as a 20% improvement in tender and swollen joint counts and a 20% improvement in 3 of the following:
- patient global assessment of disease activity (100mm VAS, 0 = very well to 100 = very poor)
- investigator global assessment of disease activity (Likert Scale, 0 = very well to 4 = very poor)
- Stanford Health Assessment Questionnaire (HAQ) Disability Index (Likert Scale, 0 = no difficulty to 4 = unable to do)
- Patient global assessment of pain (100mm VAS, 0 = no pain to 100 = extreme pain)
- C-reactive protein levels.

The primary end-point for the remaining 44-week period was assessed with global measurements (details not provided).[48]

### Table IV
Results of 2 randomised, double-blind clinical trials comparing the efficacy of rofecoxib (R) with that of naproxen (N) or placebo (PL) in patients with rheumatoid arthritis

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Trial duration (mo)</th>
<th>Dosage (mg/day)</th>
<th>Improvement from baseline (%)</th>
<th>ACR 20 responders (%)</th>
<th>ACR 20 responders and completers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>global disease activity score</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>patient assessment</td>
<td>investigator assessment</td>
<td>MHAQ</td>
</tr>
<tr>
<td>Bombardier et al.[49]</td>
<td>R 4047</td>
<td>13*</td>
<td>50 od</td>
<td>26</td>
<td>26</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>N 4029</td>
<td></td>
<td>500 bid</td>
<td>27</td>
<td>28</td>
<td>20</td>
</tr>
<tr>
<td>Schnitzer et al.[47]</td>
<td>R 158</td>
<td>2</td>
<td>5 od</td>
<td>35</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R 171</td>
<td></td>
<td>25 od</td>
<td>49*</td>
<td>44*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>R 161</td>
<td></td>
<td>50 od</td>
<td>53*</td>
<td>50*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PL 168</td>
<td></td>
<td></td>
<td>35</td>
<td>32</td>
<td></td>
</tr>
</tbody>
</table>

a The primary end-point of this trial was clinical upper gastrointestinal events.

b The median duration of follow up was 9 months.

ACR 20 = 20% improvement in various American College of Rheumatology parameters; bid = twice daily; MHAQ = Modified Health Assessment Questionnaire; * p < 0.001 vs placebo; od = once daily.
tively. Relative to baseline, rofecoxib recipients had a 19% improvement in the Modified Health Assessment Questionnaire score compared with a 20% improvement for naproxen (table IV). Low withdrawal rates due to lack of efficacy were seen for both treatments (6.3 for rofecoxib vs 6.5% for naproxen).

After 8 weeks of therapy, rofecoxib 25 and 50mg were significantly better in terms of ACR 20 response and study completion than placebo (p = 0.001) in 658 patients with rheumatoid arthritis (table IV); there were no significant differences when patients were stratified for methotrexate use. The proportion of patients achieving an ACR 20 response and completing the study was 32, 34, 44 and 50% for the placebo, and rofecoxib 5, 25 and 50mg groups, respectively (table IV). Rofecoxib 25 and 50mg were also significantly more effective than placebo for the individual efficacy measurements: patient global assessment of pain (mean change on the VAS of ≈ 25 vs 15mm), patient global assessment of disease activity (= 28 vs 18mm) and investigator global assessment of disease activity (mean change on the Likert scale of ≈ 1.2 vs 0.9) [p < 0.001]. After 8 weeks, placebo and rofecoxib 5mg recipients were reassigned to either rofecoxib 25 or 50mg or naproxen 500mg twice daily for an additional 44 weeks. After 1 year, the improvements in the 8-week end-points were maintained. Global efficacy was similar for rofecoxib 25 and 50mg and naproxen (data not reported). There were no differences between those patients who were reassigned and those continuously receiving the same treatment.

5. Tolerability

Rofecoxib is generally well tolerated in the treatment of osteoarthritis, acute dental pain, post-operative surgical pain, primary dysmenorrhea and rheumatoid arthritis. In this section, the tolerability of rofecoxib is discussed in comparison with that of traditional NSAIDs, analgesics and the selective COX-2 inhibitor celecoxib with regard to its GI, cardiovascular and general tolerability profiles.

5.1 Upper Gastrointestinal Adverse Events

In patients with either osteoarthritis or rheumatoid arthritis, rofecoxib is associated with a lower incidence of upper GI perforations, ulcerations and bleeding (PUBs) than non COX-selective NSAIDs.

Based on the results of a meta-analysis of 8 double-blind, randomised studies in over 5000 patients with osteoarthritis, fewer rofecoxib recipients withdrew from further study because of an upper GI adverse event [3.5 vs 4.8% for traditional NSAIDs (ibuprofen, diclofenac and nabumetone)] and a significantly lower 6-month incidence of cumulative dyspeptic-type GI events was recorded than with traditional NSAIDs (23.5 vs 25.5%, p = 0.02). A significant difference between rofecoxib and the NSAIDs in the incidence of PUBs was apparent as early as 6 weeks after the initiation of treatment [relative risk (RR) for rofecoxib vs traditional NSAIDs 0.21; 95% confidence interval (CI), 0.06 to 0.67; p = 0.004]. At 12 months, the rate per 100-patient years for GI adverse events was also significantly lower for rofecoxib recipients (116.9 vs 138.1, p = 0.01) than for traditional NSAID recipients. The RR for rofecoxib versus traditional NSAIDs was 0.88 (95% CI, 0.80 to 0.97, p = 0.01).

In over 8000 patients with rheumatoid arthritis enrolled in the VIGOR study (section 4.3), 2.2% of all patients had a confirmed upper GI event (median duration of follow-up was 9 months). In 30% of these patients this event was complicated; an additional 0.2% had GI events that were unconfirmed. A significantly (p < 0.001) lower overall incidence of confirmed upper GI events was reported with once daily rofecoxib 50mg (1.4%) than with naproxen 500mg twice daily (3%) [fig. 3]; this result was regardless of the presence or absence of Helicobacter pylori. However, a significant difference in the RR of clinical events emerged between H. pylori-positive and -negative patients (p = 0.04, data not presented). Active gastritis caused by H. pylori is associated with COX-2 expression; therefore it is important to determine the tolerability of a COX-2 inhibitor in the...
presence of *H. pylori*.[52] The RR of confirmed upper GI events for rofecoxib versus naproxen was 0.5 (95% CI, 0.3 to 0.6; \( p < 0.001 \)). For complicated confirmed upper GI events the RR was 0.4 (95% CI, 0.2 to 0.8; \( p = 0.005 \)). For rofecoxib versus naproxen patients, the RR of complicated upper GI bleeding was 0.4 (95% CI, 0.2 to 0.7; \( p = 0.004 \)); the RR of bleeding beyond the duodenum was 0.5 (95% CI, 0.2 to 0.9; \( p = 0.03 \)).[49]

In this study, the overall incidence of patients receiving either rofecoxib or naproxen reporting a GI adverse event was 36%.\(^{[53]}\) Compared with naproxen, rofecoxib was associated with the use of fewer GI protective agents (25.5% vs 32.2%, \( p < 0.001 \)), fewer GI procedures (12.4% vs 15.8%, \( p = 0.01 \)) and rofecoxib recipients were hospitalised for PUBs less often (1.2% vs 2.3%, \( p = 0.02 \)) in a subset of patients who reported GI adverse events.\(^{[53]}\)

### 5.1.1 Endoscopy Studies

In patients with osteoarthritis, the cumulative 24-week incidence of gastroduodenal ulceration \( \geq 3 \text{mm} \) was approximately 3 to 4 times lower with once daily rofecoxib 25 or 50mg than with ibuprofen 2400 mg/day (\( p < 0.001 \); table V).\(^{[54,55]}\) Endoscopy performed at baseline, 6, 12 and 24 weeks confirmed a lower incidence of gastroduodenal ulceration with rofecoxib beginning at least 6 weeks after treatment was initiated.\(^{[54]}\) In addition, the cumulative 24-week incidence of gastroduodenal ulcers \( \geq 5 \text{mm} \) was lower with rofecoxib 25 or 50mg therapy (4.6 and 11.6% vs 30.2% for ibuprofen; \( p < 0.001 \)).\(^{[54]}\)

### 5.2 Cardiovascular Adverse Events

It has been hypothesised that rofecoxib, a selective COX-2 inhibitor which has little or no effect on platelet function (section 2.4), may increase the risk of cardiovascular adverse events.\(^{[33]}\)

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**Fig. 3.** Incidence of confirmed upper gastrointestinal (GI) events in patients with rheumatoid arthritis randomised to either rofecoxib 50mg daily (\( n = 4047 \)) or naproxen 500mg twice daily (\( n = 4029 \)).\(^{[49]}\) The median duration of follow-up was 9 months. The cause or source of bleeding in rofecoxib recipients was gastric or duodenal ulcers in 5 patients each, and another upper GI source in 3 patients (not specified). In naproxen recipients, 16 had gastric ulcers, 9 had duodenal ulcers and other upper GI sources (not specified) were the cause or source of bleeding in 7. Individual \( p \)-values were not reported.
In the VIGOR study, mortality rates were 0.5 vs 0.4% for rofecoxib and naproxen, respectively, in over 8000 patients with rheumatoid arthritis. The mortality rate from cardiovascular causes was 0.2% for both treatment groups. Myocardial infarctions occurred in 0.4% of rofecoxib and 0.1% of naproxen recipients (95% CI for the difference, 0.1 to 0.6; RR 0.2, 95% CI, 0.1 to 0.7). However, 38% of patients who had a myocardial infarction met the US Food and Drug Administration criteria for the use of aspirin as secondary prophylaxis but were not taking low-dose aspirin therapy. When these patients were excluded from the analysis, the rate of myocardial infarction was not significantly different between the groups (0.2% for rofecoxib vs 0.1% for naproxen).

In a 1-year study of 784 patients with osteoarthritis of the hip or knee, which included patients with cardiovascular risk factors, the incidence of thromboembolic cardiovascular events (myocardial infarction, stroke, transient ischaemic attack and peripheral arterial occlusions) was numerically lower with rofecoxib 12.5 or 25mg than with diclofenac 150 mg/day (1.5, 2.3 and 3.4%, respectively).

A meta-analysis examined cardiovascular data from 19 phase IIb to V studies which enrolled a total of >28 000 patients with either osteoarthritis, rheumatoid arthritis, chronic low back pain or Alzheimer's Disease (interim data only). The RR of an Antiplatelet Trialists' Collaboration (APTC) event, defined as the combination of cardiovascular or unknown death, stroke or myocardial infarction, was 0.59 for naproxen compared with rofecoxib (95% CI, 0.37 to 0.94). In comparison with rofecoxib the RR of an APTC event for other NSAIDS which have a less sustained effect on platelet inhibition, such as diclofenac, ibuprofen and nabumetone, was 1.27 (95% CI 0.64 to 2.5).

### Table V. Endoscopic* cumulative incidence over 24 weeks of gastroduodenal ulceration* by intention-to-treat life-table analysis in 2 randomised, controlled trials in patients with osteoarthritis

<table>
<thead>
<tr>
<th>Reference [study duration (wk)]</th>
<th>Treatment (mg/day)</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawkey et al. [54] [24]</td>
<td>R 25 [373]</td>
<td>9.9*</td>
</tr>
<tr>
<td></td>
<td>R 50 [360]</td>
<td>12.4*</td>
</tr>
<tr>
<td></td>
<td>I 2400* [354]</td>
<td>46.8</td>
</tr>
<tr>
<td>Laine et al. [54] [24]</td>
<td>R 25 [186]</td>
<td>9.6*</td>
</tr>
<tr>
<td></td>
<td>R 50 [178]</td>
<td>14.7*</td>
</tr>
<tr>
<td></td>
<td>I 2400* [167]</td>
<td>45.8</td>
</tr>
</tbody>
</table>

* Endoscopy was performed at baseline, 6, 12 and 24 weeks.
* Defined as a mucosal break with ≥3mm unequivocal depth.
* Patients were permitted to take paracetamol (acetaminophen) (≤2600 mg/day) and non-NSAID pain medications.
* Administered as 800mg 3 times daily.

NSAID = nonsteroidal anti-inflammatory drugs; I = ibuprofen; R = rofecoxib; * p < 0.001 vs ibuprofen.

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5.3 General Tolerability Profile

5.3.1 Osteoarthritis

In approximately 2200 patients with osteoarthritis treated with rofecoxib in clinical trials, adverse events reported with an incidence of ≥3% were epigastric discomfort, upper respiratory tract infection (URTI), headache, viral syndrome, sinusitis, diarrhoea and nausea.[28,30,33,58]

Compared with placebo, in 1 study rofecoxib 25 or 125mg once daily was generally associated with a higher incidence of adverse events [fig. 4].[28] Lower extremity oedema was reported with both doses of rofecoxib (2.7 and 6.8%) but not with placebo.

Interestingly, compared with diclofenac 50mg 3 times daily in a randomised, double-blind trial, rofecoxib 12.5 or 25mg once daily was associated with a higher incidence of URTI (23.9 and 25.7 vs 17.9%), sinusitis (8.9 and 7.4 vs 7.1%) and heartburn (5.4 and 5.1 vs 3%), although these differences were not considered to be significant.[33] The lowest incidence of nausea occurred with rofecoxib 12.5mg (6.2 and 7.4 vs 9.7% with diclofenac) and the highest incidence of diarrhoea occurred with rofecoxib 25mg (6.9 and 12.1 vs 10.4%).[33]

When diclofenac 50mg was combined with misoprostol 200μg administered twice daily (n = 241) in a multicentre, randomised, double-blind trial, a higher incidence of adverse events was associated with this combination than with rofecoxib 12.5mg once daily (n = 242).[58] Abdominal pain (13.3 vs 8.7%, 95% CI –12.3 to 2.0), URTI (5 vs 2.9%, 95% CI –8.2 to 2.7), diarrhoea (19.9 vs 6.2%, 95% CI –21.4 to –6.9), dyspepsia (10.8 vs 2.9%, 95% CI –14.5 to –2.4), epigastric discomfort (11.2 vs 3.7%, 95% CI –14.3 to –1.8), headache (9.5 vs 5.8%, 95% CI –10.8 to 2.1), and nausea (10.4 vs 8.3%, –9.6 to 4.2) were all reported with a higher incidence with diclofenac/misoprostol than rofecoxib.[58]

In comparison with ibuprofen, epigastric discomfort occurred with a lower incidence with daily rofecoxib 12.5 or 25mg (5.7 and 5.8 vs 8%). The incidence of diarrhoea was similar between the 2 agents (4.5 and 5 vs 5.2%, respectively) and the highest incidence of nausea occurred with rofecoxib 25 mg/day (6.6% compared with 2.9% for rofecoxib 12.5 mg/day and 3.6% for ibuprofen 800mg 3 times daily).[30]

Rofecoxib 12.5 and 25mg was generally well tolerated in patients aged >80 years.[36] The most common adverse events were lower extremity oedema (7.6 and 5.4 vs 4.3% for nabumetone 1500mg), URTI (5.1 and 7.1 vs 6.1%), constipation (1.7 and 5.4 vs 0.9%), diarrhoea (5.1 and 3.6 vs 7.8%), nausea (3.4 and 5.4 vs 4.3%) and headache (1.7 and 5.4 vs 2.6%).[36] Mean changes in blood pressure were similar for all treatment groups.

Rofecoxib contains a sulphur atom as part of a methyl sulphonyl moiety, but is chemically distinct from the sulfonamides.[59] The incidence of allergic reactions, in 237 patients with osteoarthritis and a history of allergy to sulfonamides or sulphur containing compounds, was lower with rofecoxib than with either placebo or conventional NSAIDs (9.9 vs 15.8 and 16.8%) over a mean treatment duration of 5.5 months (reported as an abstract).[59]

5.3.2 Acute Pain

Post-surgical Dental Pain

In comparison with placebo, ibuprofen 400 mg/day and celecoxib 200 mg/day, rofecoxib 50 mg/day was generally associated with a lower incidence of nausea (20, 17.4, 12.2 and 8.9%, respectively),[40] headache (13.3, 8.7, 13.2 and 12.2%) and vomiting (13.3, 8.7, 6.6 and 1.1%; p < 0.001 for rofecoxib vs placebo)[40] in the treatment of post-surgical dental pain.[9,39,40] With the exception of vomiting there were no significant differences between the groups.[40] Slightly elevated ALT and AST levels were reported in all treatment groups (with the exception of normal AST levels for ibuprofen).[39,40] Glycosuria was recorded in 2% of rofecoxib recipients.[39]

Postoperative Surgical Pain

Rofecoxib was similarly well tolerated in the treatment of orthopaedic surgical pain; constipation, nausea and fever were the most common adverse events.[42] Rofecoxib 25 or 50 mg/day had a lower incidence of constipation (10.7 and 20.4%)
than either placebo (28.3%) or naproxen sodium 550 mg/day (21.8%); however, the incidence of nausea was higher with rofecoxib 50 mg/day (20.4%) than rofecoxib 25 mg/day (10.7%), placebo (11.3%) or naproxen sodium (16.4%). The incidence of fever was highest with placebo (20.8%) followed by rofecoxib 50 mg/day (9.3%) then naproxen sodium (5.5%) and rofecoxib 25 mg/day (5.4%). The significance of these differences was not reported.

Lower incidences of dizziness and headache were reported with rofecoxib 25 and 50 mg/day (5.4 and 1.9%, respectively, for dizziness and 1.8 and 1.9% for headache) compared with naproxen (10.9 and 7.3%, respectively) and placebo (11.3 and 7.5%). However, rofecoxib 50 mg/day was associated with a higher incidence of insomnia (11.1%) and pruritus (5.6%) than either rofecoxib 25 mg/day (10.7 and 1.8%, respectively) or naproxen sodium (7.3 and 3.6%, respectively). Oedema and hypertension and mean changes in body-weight and blood pressure were reported with a similar incidence across all treatment groups.

However, in this study naproxen sodium was given as a single dose on day 1, followed by placebo for the remainder of the trial; similarly rofecoxib was reduced to 25 mg/day in some recipients with no washout period (section 4.2.3). These results should therefore be interpreted with caution.

Primary Dysmenorrhoea

In patients with primary dysmenorrhoea, the primary drug-related adverse events were nausea and dry mouth. These events occurred in 6 to 11% of patients receiving rofecoxib 25 or 50 mg compared with 3 and 9% of placebo and naproxen sodium 550 mg recipients, respectively (p < 0.05 for rofecoxib vs placebo).

5.3.3 Rheumatoid Arthritis

In 658 patients with rheumatoid arthritis, the most common adverse events (occurring in >3% of any treatment group) associated with rofecoxib 5, 25 and 50 mg once daily for 8 weeks were diarrhoea (7, 4.7 and 3.7%, respectively vs 3% for placebo), headache (4.4, 5.8 and 4.3% vs 6.5%), asthenia/fatigue (3.2, 4.1 and 2.5% vs 4.8%) and dizziness (0.6, 7 and 3.7% vs 1.8%). A greater number of 50 mg recipients experienced a rash (5.6 vs 1.2% for placebo), most of which were mild, unrelated to rofecoxib and resolved during treatment. The incidences of lower-extremity oedema and hypertension were low and were similar between all treatment groups.

6. Pharmacoeconomic Considerations

There are few formal data on the pharmacoeconomics of rofecoxib. Data from 1 study reported as an abstract show that, in the treatment of patients with osteoarthritis aged ≥65 years, rofecoxib has a slightly higher acquisition cost than other commonly used NSAIDs (1.60 vs 1.67 per patient per day, 2000 Canadian (Can) dollars); this leads to an incremental annual cost of $24.45 per patient using rofecoxib. These figures may double when rofecoxib is used to treat acute pain because higher dosages are used. However, rofecoxib is associated with a reduction of 0.0109 PUBs per patient per year, resulting in costs per PUB averted of $Can2247. These rates were sensitive to changes in prophylactic GI medication rates and drug costs and were robust over a range of model assumptions (no data provided).

In patients with rheumatoid arthritis with a low risk (=0.4%) of developing NSAID-induced GI complications, >500 patients would need to be treated with rofecoxib to prevent 1 ulcer complication (assuming rofecoxib reduces the risk by 50%). Furthermore, based on 1999 US data the yearly incremental cost of rofecoxib 25 mg/day compared with a generic NSAID such as naproxen is $US763 per patient, which equates to approximately $US400 000 per 500 patients. Conversely, however, higher risk patients, such as those aged ≥75 years with a prior history of ulcer and GI bleeding, have an approximate 5% risk of developing a complicated GI ulcer while taking an NSAID. Under the same assumptions, 40 patients would need to be treated with rofecoxib in order to...
prevent 1 ulcer complication, at a yearly incremental cost of $US30 000.[61]

7. Dosage and Administration

In the US, rofecoxib is approved for the treatment of osteoarthritis and acute pain, which includes dental pain, postoperative surgical pain and primary dysmenorrhoea in adults.[19] In the UK, France, Germany and several other European countries, rofecoxib is approved for the symptomatic relief of osteoarthritis.

Oral rofecoxib can be administered either as tablets (12.5 or 25mg) or as a suspension (12.5mg in 5ml or 25mg in 5ml).[19]

Based on the US prescribing information for the treatment of osteoarthritis, the recommended initial dosage of oral rofecoxib is 12.5mg once daily. This dosage may be increased to a maximum of 25mg per day.[19] For the treatment of acute pain, the recommended initial dosage of oral rofecoxib is 50mg once daily. Subsequent doses of rofecoxib should be 50mg once daily as needed. In this indication, rofecoxib has not been evaluated for longer than 5 days.[19] Single doses of up to 1000mg have been evaluated in clinical trials in patients with dental pain; however there are few tolerability data available at this high dose.[9] In contrast with most traditional NSAIDs, rofecoxib may be administered with or without food.[19]

Rofecoxib is not yet approved for use in patients with rheumatoid arthritis. However, in clinical trials in these patients, rofecoxib 25 or 50mg once daily was used (section 4.3.1).[47,49]

In patients aged ≥65 years, no dosage adjustment for rofecoxib is necessary; however, treatment should be initiated at the lowest possible dose.[19]

Rofecoxib is contraindicated in patients with known hypersensitivity to rofecoxib. For a list of drug interactions, warnings and precautions (see also section 3.2) associated with rofecoxib therapy, see table VI.

8. Place of Rofecoxib in the Management of Osteoarthritis, Acute Pain and Rheumatoid Arthritis

Arthritis is one of the most common chronic conditions in developed countries.[62] It is estimated that approximately 1 in 6 people (about 43 million) in the US are affected by some form of arthritis.[63] Osteoarthritis is by far the most prevalent form of arthritis, affecting an estimated 22.7 million people in the US.[63-65] Osteoarthritis is a degenerative joint disease characterised by pain and/or limitation of movement to the affected joints.[66] Rheumatoid arthritis, an autoimmune disease of unknown aetiology, affects approximately 1% of the adult population.[67] In the US, this is equivalent to 2.1 million people.[63] The disease generally follows a fluctuating disease course characterised by joint inflammation and sometimes multisystem involvement.[67]

Age is a major factor in the increasing prevalence of arthritis.[62,63] With an increased life expectancy over the past 100 years of approximately 30 years, adults aged ≥65 years, who accounted for 13% of the population in 1990, are expected to represent 22% of the population by the year 2030.[63] At the same time, the prevalence of arthritis is estimated to increase by 28% in the US by the year 2020. In addition, 65% of the population will be affected by an arthritis-associated disability.[62] This is estimated to have a significant impact on society in terms of medical care and lost wages due to arthritis; the annual cost to society was estimated to be approximately $US95 billion in the year 2000.[63]

At present, preventative or curative therapies for these 2 types of arthritis are not available. Treatment options therefore largely aim to relieve the symptoms of pain and inflammation. The approach recommended by the ACR for the management of osteoarthritis of the hip and knee includes non-pharmacological therapy, such as patient education, physical therapy, aerobic exercise and occupational therapy, combined with drug treatment. Current pharmacological management guidelines recommend treatment with oral nonopioid analge-
sics, nonselective NSAIDs plus gastroprotective agents or a COX-2 selective inhibitor.\(^{[65]}\) Topical analgesics may be useful for patients not responsive to, or not wishing to take, systemic analgesics. Intra-articular steroid injections may also be used cautiously in patients with osteoarthritis of the knee.\(^{[65]}\) Nonpharmacological measures are considered, by the ACR, to be the cornerstone of osteoarthritis management and should be maintained throughout the treatment period.

Similarly the European League for Arthritis and Rheumatism (EULAR) recommend the combination of pharmacological and nonpharmacological treatment modalities for the management of osteo-

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Table VI. List of warnings, precautions and drug interaction details for rofecoxib\(^{[19]}\)

<table>
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<th>Warnings</th>
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<tr>
<td><strong>Gastrointestinal effects</strong></td>
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<td><strong>Anaphylactic reactions</strong></td>
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<td><strong>Advanced renal disease</strong></td>
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<td><strong>Pregnancy</strong></td>
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<th>Precautions</th>
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<td><strong>Hepatic effects</strong></td>
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<td><strong>Renal effects</strong></td>
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<td><strong>Haematological effects</strong></td>
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<td><strong>Cardiovascular effects</strong></td>
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<td><strong>Corticosteroid therapy</strong></td>
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<td><strong>Pre-existing asthma</strong></td>
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<th>Drug interactions</th>
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<td><strong>ACE inhibitors</strong></td>
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<td><strong>Aspirin</strong></td>
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<td><strong>Methotrexate</strong></td>
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<td><strong>Rifampicin (rifampin)</strong></td>
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<td><strong>Warfarin</strong></td>
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<td><strong>Lithium</strong></td>
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<td><strong>Cimetidine</strong></td>
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\(\text{ACE} = \text{angiotensin converting enzyme}; \ \text{AUC} = \text{area under the concentration-time curve from time zero to 12 hours}; \ \text{C}_{\text{max}} = \text{maximum plasma concentration}; \ \text{GI} = \text{gastrointestinal}; \ \text{NSAIDs} = \text{nonsteroidal anti-inflammatory drugs}.\)
It is recommended that treatment is initiated with paracetamol; this drug is also the preferred long term oral analgesic. However, NSAIDs are recommended for those patients who are unresponsive to paracetamol. Intra-articular steroid injections are indicated for acute knee pain.

The ACR recommends treatment for rheumatoid arthritis be initiated with NSAIDs and followed with disease-modifying antirheumatic drugs for patients with persistent active disease. Low-dose oral glucocorticoids and glucocorticoid injections are also effective in providing pain relief. However, it must be noted that these guidelines were prepared prior to the availability of COX-2 specific inhibitors.

NSAIDs are the most widely used agents for the treatment of arthritis and acute pain, providing effective relief from pain and inflammation. However, NSAID use is associated with a high incidence of GI complications; it is estimated that approximately 2 to 4% of NSAID users will have a serious adverse GI event per year. Worldwide sales of NSAIDs totalled $US5.7 billion in 1995; hospitalisations for NSAID-related GI complications reached 200 000 to 400 000 per year in the US at a cost of $US0.8 to 1.6 billion.

Concomitant use of NSAIDs plus sucralfate, histamine H₂-receptor antagonists, prostaglandin analogues or proton pump inhibitors have to some degree reduced the incidence of duodenal ulcers. In an attempt to reduce the incidence of gastric ulceration, a prostaglandin analogue, misoprostol, has been formulated in combination with diclofenac or naproxen; however, this treatment approach led to increases in treatment costs and treatment-limiting adverse events, such as diarrhoea. As neither approach sufficiently reduced the incidence of GI complications, efforts have turned towards developing NSAIDs with improved GI tolerability.

Traditional NSAIDs act by inhibiting the COX enzymes involved in prostaglandin synthesis. COX-1, the constitutive isoform, is involved in the synthesis of prostaglandins, which regulate normal cell activity, specifically within the GI mucosa, platelets and kidneys. The inducible form, COX-2, is generally induced in response to inflammatory stimuli and is thought to be primarily responsible for the therapeutic effects of NSAIDs. However, COX-2 also has diverse physiological and pathophysiological roles in specific areas of the brain, kidney and uterus. Most traditional NSAIDs inhibit both COX-1 and -2 enzymes to varying degrees, possibly explaining the wide range of effects seen with different agents. The discovery of the COX-2 isoform prompted the search for agents which are COX-2 selective and therefore possess anti-inflammatory and analgesic properties without the serious GI adverse effects. One such agent is rofecoxib, a highly selective COX-2 inhibitor which has no perceptible effect on the COX-1 isoenzyme at doses 20 to 80 times those recommended for various indications.

In well-controlled clinical trials, rofecoxib has been evaluated in patients with osteoarthritis, acute pain and rheumatoid arthritis. In the treatment of osteoarthritis of the hip and/or knee, rofecoxib 12.5 and 25 mg/day effectively provided symptom relief and was significantly more effective than placebo and better than or similar to other NSAIDs. Additionally, rofecoxib has shown efficacy in patients aged ≥80 years, an age group which is projected to increase rapidly over the next 20 years. Currently, >80% of those aged over 75 years show radiographic changes consistent with osteoarthritis. Future increases in this population will have major implications for healthcare providers and society as a whole.

Although not yet approved in patients with rheumatoid arthritis, rofecoxib has shown promising results in 2 large randomised, double-blind clinical trials. In over 8700 patients, rofecoxib 50 mg/day was as effective in providing symptomatic relief as the traditional NSAID naproxen 1000 mg/day and more effective than
placebo. Further clinical trials may determine the place of rofecoxib as an alternative to traditional NSAID therapy in these patients. There are currently no comparative data for rofecoxib and celecoxib, another selective COX-2 inhibitor which is approved for use in rheumatoid arthritis.

As well as having proven efficacy in managing pain and inflammation associated with chronic conditions, rofecoxib is also efficacious in an acute pain setting. Primary dysmenorrhoea is a common condition characterised as low abdominal pain occurring during menstruation in the absence of a disease such as endometriosis.\(^{[46,72]}\) Dysmenorrhoea is associated with increased endometrial prostaglandin production at the time of menstruation.\(^{[46,72]}\) However, it is currently not known whether this is mediated by COX-1 or COX-2.\(^{[46]}\) The estimated prevalence ranges from 50 to 72% of menstruating women in the US and Sweden.\(^{[46,72]}\) Treatment usually consists of nonopioid analgesics, NSAIDs, oral contraceptives or a combination of these agents.\(^{[72]}\)

Both postoperative dental and surgical pain are considered sensitive and validated models of analgesic efficacy. Postoperative dental pain may be representative of the majority of postsurgical pain situations.\(^{[73]}\)

At doses ranging from 50 to 500mg, rofecoxib effectively relieved acute pain in 3 distinct settings: postoperative dental pain, primary dysmenorrhoea and 2 of 3 postoperative surgical pain subindications (section 4.2). In these indications, rofecoxib generally provided a rapid onset of pain relief and a long duration of analgesic effect with minimal use of supplemental pain relief where required. Rofecoxib was significantly more effective than placebo and celecoxib in the treatment of dental pain and postoperative surgical pain, with the exception of similar efficacy to placebo in patients undergoing radical prostatectomy (section 4.2.2). Rofecoxib was generally similar to ibuprofen in the treatment of dental pain and naproxen sodium in treatment of both postoperative surgical pain and primary dysmenorrhoea. Despite these promising results, there are still limited data for the primary dysmenorrhoea and postoperative pain settings and more trials are needed to draw firm conclusions regarding the place of rofecoxib in the management of acute pain.

Very few trials have compared the efficacy of the 2 selective COX-2 inhibitors rofecoxib and celecoxib. Rofecoxib and celecoxib have been compared in approximately 650 patients with osteoarthritis (published as an abstract, see section 4.1.2),\(^{[32]}\) postsurgical dental pain (section 4.2.1)\(^{[40]}\) or acute pain after spinal fusion surgery (section 4.2.2).\(^{[43]}\) Preliminary data presented in abstract form suggest rofecoxib may improve both rest and night pain as well as relieving pain upon walking more effectively than celecoxib (data not reported). However, in the trials evaluating acute pain, celecoxib was administered at the dosage approved for the treatment of osteoarthritis, 200mg. Although celecoxib is not yet approved for acute pain indications, the recommended dose is likely to be higher than that currently recommended for the treatment of chronic conditions, as is the case with rofecoxib. These results must therefore be interpreted with caution and firm conclusions regarding the comparative efficacy of these 2 agents can not be made. Furthermore, with the exception of Geba et al. current literature is noticeably lacking for comparative studies on rofecoxib and celecoxib in patients with osteoarthritis, an indication for which both agents are approved.\(^{[41]}\) Fully published trials comparing the efficacy of these agents are awaited with interest.

The primary distinction between the newer, selective COX-2 agents and traditional NSAIDs is the improved GI tolerability profile. In line with its selective COX-2 status, rofecoxib 25 and 50mg was associated with a significantly lower incidence of endoscopically confirmed GI complications ≥3 and 5mm than the traditional NSAID ibuprofen in patients with osteoarthritis (section 5.1.1).\(^{[54,55]}\) Clinical data support these endoscopic findings. In 13 000 patients with osteoarthritis and rheumatoid arthritis, a lower incidence of GI adverse events was reported with rofecoxib than traditional NSAID therapy up to 1 year after the initiation of
treatment.\textsuperscript{[49,50] }Importantly, rofecoxib may provide a better treatment option than traditional NSAIDs in patients aged \( \geq 80 \) years, who are at higher risk of GI complications.\textsuperscript{[11]} Postmarketing data are likely to provide further evidence of the improved GI tolerability associated with long term use of selective COX-2 inhibitors.\textsuperscript{[69]}

There are some theoretical concerns that, because rofecoxib is selective for COX-2 and unlike traditional NSAIDs such as naproxen appears to have little or no effect on platelet function (section 2.4), at-risk patients may be more likely to experience adverse cardiovascular events.\textsuperscript{[33]} However, on the basis of several well-controlled clinical trials, this does not appear to be the case.\textsuperscript{[33,49]} In over 8000 patients with rheumatoid arthritis, there was no significant difference between rofecoxib and naproxen, a nonselective COX inhibitor, in the mortality rates attributed to cardiovascular causes (section 5.2).\textsuperscript{[49]} Although a significantly lower rate of myocardial infarction was reported with naproxen, this difference may be accounted for by the 38\% of at-risk patients who qualified for the use of low-dose aspirin as secondary prophylaxis but were not receiving this treatment. Exclusion of these patients from analysis showed no significant difference in the incidence of myocardial infarction between the 2 treatment groups.\textsuperscript{[49]} However, this difference may also be attributed to the ability of naproxen to maintain near complete inhibition of platelet function throughout its dosing interval.

Based on the results of the VIGOR study of rofecoxib, the manufacturer recommends that patients enrolled in clinical trials, who meet the criteria for secondary cardiovascular prophylaxis, be allowed concomitant aspirin.\textsuperscript{[49]} However, it is important to note that the GI tolerability of rofecoxib and concomitant aspirin is unknown. Results from the Celecoxib Long Term Arthritis Safety Study (CLASS) comparing celecoxib with traditional NSAIDs in 8059 patients with osteoarthritis or rheumatoid arthritis showed a similar incidence of upper GI complications plus symptomatic ulcers in patients receiving celecoxib and aspirin compared with traditional NSAIDs (4.7 vs 6\%, respectively).\textsuperscript{[74]}

In general, rofecoxib was well tolerated in all indications. Adverse events associated with rofecoxib and common to all indications were nausea, dizziness and headache, generally occurring in \( \geq 3\% \) of rofecoxib recipients.\textsuperscript{[28,40,42,47,58]} Interestingly, however, when diclofenac was combined with misoprostol it was associated with a higher incidence of adverse events including abdominal pain, upper respiratory tract infections and headache than rofecoxib in a randomised double-blind trial (section 5.3.1).

In conclusion, rofecoxib is at least as effective as traditional NSAID therapy in providing pain relief for both chronic and acute pain conditions. Rofecoxib provides an alternative treatment option to traditional NSAID therapy in the management of symptomatic pain relief in patients with osteoarthritis. Initial data from patients with primary dysmenorrhoea and postoperative pain are promising and further trials may confirm its place in these indications. Rofecoxib has also shown good efficacy in large well-controlled trials in patients with rheumatoid arthritis and is likely to become a valuable addition to current drug therapy for this patient population. Importantly, rofecoxib is associated with a lower incidence of GI adverse events than traditional NSAIDs making it a primary treatment option in patients at risk of developing GI complications or patients with chronic conditions requiring long term treatment.

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