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Rofecoxib

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Contents

Abstract

▲ Rofecoxib selectively inhibits cyclo-oxygenase-2 in a dose-dependent manner in humans. No significant inhibition of cyclo-oxygenase-1 is observed with rofecoxib up to doses of 1000mg.

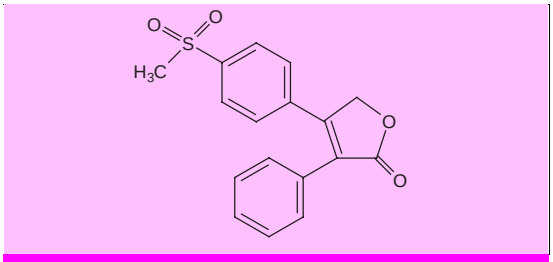
▲ In 4 large double-blind randomised trials performed in patients with osteoarthritis, rofecoxib 12.5 and 25 mg/day significantly improved physical functioning, assessed using the Western Ontario and McMasters Universities Osteoarthritis Index and patient or investigator global assessment, compared with placebo. In addition, rofecoxib showed similar clinical efficacy to that observed with diclofenac 50mg 3 times daily, ibuprofen 800mg 3 times daily and nabumetone 1500mg once daily.

▲ Rofecoxib is also an effective analgesic in patients with primary dysmenorrhoea or postoperative dental pain and demonstrates similar analgesic efficacy to that of naproxen sodium and ibuprofen.

▲ Rofecoxib is generally well tolerated. The most common adverse events associated with rofecoxib are diarrhoea, headache, nausea and upper respiratory tract infection.

▲ There was a significantly lower incidence of upper-gastrointestinal adverse events (perforations, ulcers and bleeds) in patients with osteoarthritis receiving rofecoxib 12.5, 25 or 50 mg/day than in those receiving ibuprofen, diclofenac or nabumetone.

Features and properties of rofecoxib (MK966, MK0966)	
Indications	
Osteoarthritis	Focus of this profile
Acute pain	Focus of this profile
Rheumatoid arthritis	
Mechanism of action	
Anti-inflammatory	Cyclo-oxygenase-2 inhibitor
Analgesic	
Dosage and administration	
Usual dosage in clinical trials	
Osteoarthritis	12.5 or 25 mg/day
Acute Pain	50mg loading dose; followed by 25 mg/day
Route of administration	Oral
Frequency of administration	Once daily
Pharmacokinetic profile (25 mg/day)	
Peak plasma concentration at steady state	321 μg/L
Area under plasma concentration-time curve at steady state	4018 μg/L • h
Time to peak plasma concentration	2 to 3 hours
Clearance	7.2 L/h
Terminal elimination half-life	≈17 hours
Adverse events	
Most frequent	Diarrhoea, headache, nausea, upper respiratory tract infection



Rofecoxib

Osteoarthritis is the most prevalent musculoskeletal disorder, affecting more than 70% of the population >65 years of age in the US.[1] It is characterised by subchondral sclerosis and degeneration of articular cartilage. Symptoms include joint pain, tenderness, limited movement, crepitus and variable degrees of joint inflammation. Current therapeutic strategies for osteoarthritis alleviate symptoms, particularly pain and inflammation, as currently there are no disease-modifying drugs available.[2] Paracetamol (acetaminophen) and nonsteroidal anti-inflammatory drugs (NSAID) are the drugs most commonly used for the treatment of patients with osteoarthritis.

The principal mechanism of action of NSAIDs is inhibition of cyclo-oxygenase (COX) enzymes which are involved in synthesis of prostaglandins. COX-1, the constitutively expressed isoform of the enzyme, plays a key role in prostaglandin synthesis in the gastric mucosa, platelets and kidneys. COX-2 is an inducible isoform involved in the inflammatory response. Recent evidence suggests that COX-2 inhibition is responsible for the anti-inflammatory and analgesic effects of NSAIDs, whereas inhibition of COX-1 may be associated with the adverse gastrointestinal effects.[3,4] Rofecoxib, the focus of this profile, is a new COX-2 inhibitor that is being developed for use in patients with osteoarthritis and/or acute pain.

1. Pharmacodynamic Profile

Inhibition of Cyclo-Oxygenase Isoforms

- Rofecoxib selectively inhibited COX-2 activity in a dose-dependent manner *ex vivo*.[5] Although rofecoxib effectively inhibited COX-2 activity [dose required to inhibit enzymatic activity by 50% (IC_{50}) was 0.77 μmol/L; 25 to 1000mg dose range], no significant inhibition of COX-1 activity was observed with doses of up to 1000mg. In contrast, indomethacin showed dose-dependent inhibition of both COX-1 (IC_{50} 0.09 μmol/L) and COX-2 activity (IC_{50} 0.30 μmol/L). Volunteers received a single oral dose of rofecoxib 5 to 1000mg or placebo (n = 8) in a dose-escalating manner or a single dose of indomethacin 5 to 75mg or placebo (n = 9) in this double-blind, crossover, randomised study.[5] Blood samples were collected immediately before and 1.25, 4 and 8 hours after treatment. COX-1 activity was determined *ex vivo* by measuring the serum concentration of thromboxane-2 (TBX_2), and COX-2 activity by assaying the concentration of prostaglandin E_2 (PGE_2) in whole blood 24 hours after incubation with lipopolysaccharide (LPS).

- At steady state, rofecoxib 25 to 375 mg/day specifically inhibited COX-2 activity *ex vivo*, but showed no significant effect on COX-1 activity in healthy volunteers.[6] The mean maximum inhibition (I_{max}) of LPS-stimulated PGE_2 at day 1 was 51, 90, 90, 92 and 14% with rofecoxib 25, 100, 250 and 375 mg/day and placebo, respectively, and after 14 days I_{max} values were 77, 98, 96, 97, and 37%. In contrast, there was no significant effect on TBX_2 production with any dose of rofecoxib.

- In direct comparisons *ex vivo*, rofecoxib specifically inhibited COX-2 activity (LPS-stimulated PGE_2 synthesis); but unlike NSAIDs (meloxicam, diclofenac, ibuprofen, and naproxen sodium) there was minimal inhibition (5 to 9%) of COX-1 activity (TBX_2 production in clotting blood) in 76 healthy female volunteers (fig. 1).[7] Subjects received treatment for 5 days and on the morning of day 6; blood samples were collected 2, 4 and 8 hours after the last dose.

Gastrointestinal Effects

- Healthy volunteers were significantly less likely to develop gastrointestinal ulcers with rofecoxib 250mg once daily (n = 49) than with ibuprofen

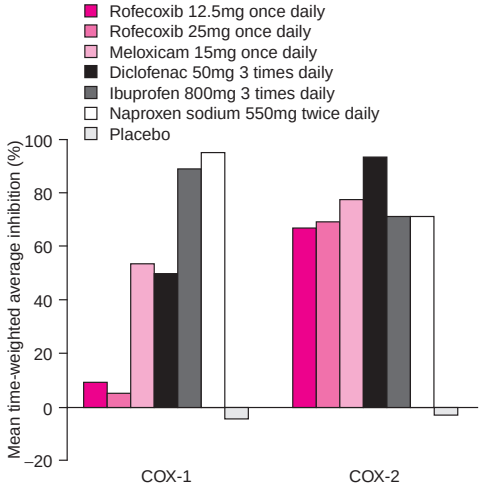


Fig. 1. Comparative effects of rofecoxib and NSAIDs on COX-1 and COX-2 activity in 76 healthy female volunteers.[7] Volunteers received treatment for 5 days and on the morning of day 6; blood samples were collected 2, 4 and 8 hours after the last dose. Serum concentrations of thromboxane-2 were measured *ex vivo* to assess COX-1 activity; COX-2 activity was assessed at the same time by measuring lipopolysaccharide-stimulation of prostaglandin E_2 synthesis in whole blood. Statistical significance was not reported. **COX-1** = cyclo-oxygenase-1; **COX-2** = cyclo-oxygenase-2; **NSAIDs** = nonsteroidal anti-inflammatory drugs.

800mg 3 times daily (n = 51; $p < 0.001$) or aspirin 650mg 4 times daily (n = 17; $p < 0.001$) administered for 7 days.[8] Endoscopic evaluation at day 7 also showed that there was no significant difference between rofecoxib and placebo (n = 50).

- Unlike indomethacin, which significantly increased intestinal permeability compared with placebo ($p < 0.001$), rofecoxib showed no effect on the same parameter in healthy volunteers.[9] The effect of indomethacin 50mg 3 times daily was also significantly greater ($p \leq 0.001$) than that observed with rofecoxib 25 or 50mg once daily. In this double-blind, randomised, crossover study, intestinal permeability was assessed in 39 healthy volunteers by measuring urinary recovery of [^{51}Cr]edetic acid and L-rhamnose for 5 hours after a 7-day oral course of rofecoxib, indomethacin or placebo. Treatments were separated by a 7-day washout period.

- Rofecoxib resulted in less faecal blood loss than ibuprofen and similar faecal blood loss to that observed with placebo in 67 healthy volunteers.[10] In this double-blind randomised study, faecal blood loss was assessed, using ^{51}Cr-labelled red blood cells, before and during a 28-day treatment course of oral rofecoxib 25 or 50mg once daily, ibuprofen 800mg 3 times daily or placebo.

Antipyretic Activity

- Rofecoxib showed similar antipyretic activity to ibuprofen in patients with upper respiratory tract infections.[11] Both ibuprofen and rofecoxib had significantly better antipyretic activity than placebo ($p < 0.001$). 93 patients with fever (38 to 40°C) received a single oral dose of rofecoxib 12.5 or 25mg, ibuprofen 400mg or placebo in a randomised study. The primary end-point was mean change in oral temperature 4 hours after treatment.

2. Pharmacokinetic Profile

Healthy Volunteers

- Peak plasma concentration (C_{max}) with a single oral dose of rofecoxib 25mg was 207 μg/L; with multiple 25mg doses, C_{max} at steady state was 321 μg/L and occurred after 4 days.[12] The median time to reach C_{max} (t_{max}) for rofecoxib was 2 to 3 hours; the plasma concentration-time profile exhibited multiple peaks.[12]

- The area under the plasma concentration-time curve (AUC) with a single oral dose of rofecoxib 25mg was 3268 μg/L · h; with multiple 25mg doses, steady-state AUC_{24h} was 4018 μg/L · h.[12]

- C_{max} and AUC values were relatively dose-proportional with therapeutic doses of rofecoxib, but with doses >50mg there was a decrease in dose-proportionality which is thought to be due to the low solubility of rofecoxib.[12]

- The mean oral bioavailability of rofecoxib 12.5, 25 and 50mg was approximately 93%.[12]

• With rofecoxib plasma concentrations 0.05 to 25 mg/L approximately 87% was bound to human plasma proteins.[12] The apparent volume of distribution at steady state (V_{ss}) was approximately 91L with a 12.5mg dose and 86L with a 25mg dose.

• Plasma clearance of rofecoxib 12.5 and 25mg was approximately 8.46 and 7.2 L/h, respectively.[12] The effective half-life of rofecoxib (based on steady-state levels) was approximately 17 hours.[12] The majority of rofecoxib was eliminated by hepatic metabolism, with less than 1% recovered unchanged in the urine.[12] The principal metabolites were *cis*-dihydro and *trans*-dihydro derivatives and a glucuronide of the hydroxy derivative.

Special Populations

• AUC values increased by 34% in people >65 years of age compared with younger people; no pharmacokinetic investigations have been undertaken in patients <18 years of age.[12]

• There were no effects on pharmacokinetic parameters in patients with mild hepatic insufficiency (Child-Pugh score ≤6) compared with healthy volunteers. In patients with moderate hepatic insufficiency (Child-Pugh score >6 and ≤9), AUC values increased by about 69%; there are no studies in patients with severe hepatic failure.

3. Therapeutic Trials

Osteoarthritis

Several large double-blind randomised trials have been performed with oral rofecoxib in patients with knee or hip osteoarthritis. One of these was a dose-finding trial[13] and the others compared rofecoxib with the NSAIDs diclofenac,[14] ibuprofen[15,16] or nabumetone.[17] Patients selected for 2 of these comparative trials[14,15] included those with increased pain following NSAID withdrawal (90% of total study populations) and those with at least moderate symptoms while taking paracetamol (10%). Eligibility criteria for the other 2 comparative studies were not specified.[16,17] All trials used similar primary end-points: patient global assessment of response to therapy; investigator global assessment of disease status; and pain walking on a flat surface assessed according to the Western Ontario and McMasters Universities Osteoarthritis Index (WOMAC)[14-17] or WOMAC VA 3.0.[13] WOMAC is a multidimensional, self-administered, disease-specific, health-related, quality-of-life measure for patients with osteoarthritis that uses either a 5-point Likert scale or a 100mm visual analogue scale (VAS). All trials were presented as abstracts.

• In a dose-ranging multicentre study, oral rofecoxib 5 to 50mg once daily showed significantly greater efficacy than placebo with respect to physical functioning according to all primary and secondary end-points (including WOMAC stiffness and disability subscales; $p < 0.001$).[13] However, the efficacy of rofecoxib 12.5 (n = 144), 25 (n = 137) and 50 mg/day (n = 97) was reportedly better than that observed with 5 mg/day (n = 149).

• Rofecoxib had similar clinical efficacy to diclofenac over a 26-week period (n = 784),[14] ibuprofen over a 6-week period (n = 736 and 809),[15,16] and nabumetone over a 6-week period (n = 341)[17] according to all primary and secondary (WOMAC stiffness and functional subscales and joint stiffness) end-points; the effects of treatments on WOMAC 100mm VAS are shown in figure 2.

Acute Pain

• Oral rofecoxib 50mg demonstrated similar analgesic efficacy to naproxen sodium for all end-points measured in patients with postoperative dental pain (n = 229 and 331) in double-blind randomised dose-finding trials.[18,19] For example, single oral doses of rofecoxib 12.5, 25 or 50mg or naproxen sodium 550mg were significantly more effective than placebo ($p \leq 0.009$) in providing total pain relief (TOPAR) at 8 hours in 331 patients; rofecoxib 25 and 50mg were more effective than a 12.5mg dose ($p < 0.001$).[19] For other end-points [sum of pain intensity differences (SPID) at 8 hours, patient's global evaluation, stopwatch time to meaningful pain relief, peak pain relief, peak pain intensity differences (PID) or time to remedication], all doses of rofecoxib were significantly more effective than

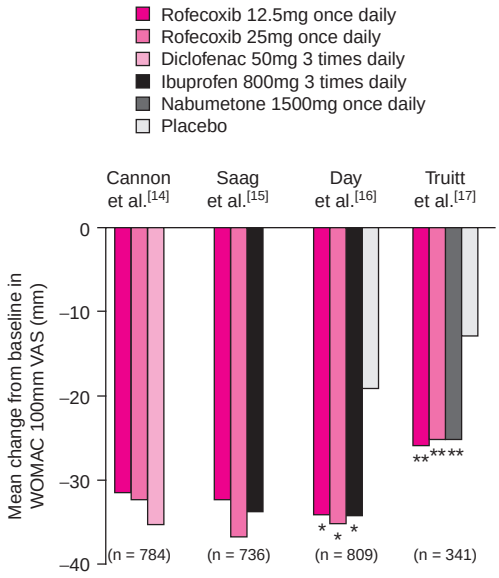


Fig. 2. Comparative efficacy of rofecoxib on physical functioning (pain walking on a flat surface; WOMAC 100mm VAS) in patients with osteoarthritis.[14-17] Baseline values for WOMAC 100mm VAS were: 26-week study by Cannon et al.[14] 76mm, 6-week study by Saag et al.[15] 74mm, 6-week study by Day et al.[16] 73mm and no baseline value was specified the for 6-week study by Truitt et al.[17] No significance data were provided for the studies by Cannon et al.[14] and Saag et al.[15] **WOMAC** = Western Ontario and McMasters Universities Osteoarthritis Index; **VAS** = visual analogue scale; *p ≤ 0.009 vs placebo; **p ≤ 0.001 *vs* placebo.

placebo (p ≤ 0.009), and 25 and 50mg doses were more effective than a 12.5mg dose (p ≤ 0.006).

• In addition, oral rofecoxib had similar analgesic efficacy to ibuprofen in double-blind, randomised trials in patients with moderate to severe postoperative dental pain.[5,20] For example, according to 3 measures (time-weighted SPID and TOPAR, and mean patient global evaluation), single doses of rofecoxib 50 (n = 32) and 500mg (n = 20) and ibuprofen 400mg (n = 20) demonstrated similar efficacy and were all superior to placebo (n = 32; p < 0.001) over a 6-hour assessment period or at the time of rescue medication.[5] The median times to meaningful pain relief in patients receiving rofecoxib 50 or 500mg, or ibuprofen 400mg were also similar (1.5, 1.2 and 1.2 hours, respectively), and all were significantly shorter than the time with placebo (4.5 hours; p < 0.002).

• An initial dose of rofecoxib 50mg followed by a 25 mg/day maintenance dose showed analgesic efficacy according to all end-points in patients with primary dysmenorrhoea in 2 randomised, double-blind, placebo-controlled crossover trials (n = 63 and 127);[21,22] and was similar in efficacy to naproxen sodium.[21] In the comparative trial, for the primary end-point (TOPAR at 8 hours), analgesic efficacy with initial doses of rofecoxib 25 or 50mg was significantly better than that of placebo (p < 0.001); similarly for all other end-points (SPID 8 hours, patient's global evaluation, peak pain relief, peak PID, time to remedication, ranking of the study drugs across cycle), both initial doses of rofecoxib were significantly more effective than placebo (p ≤ 0.003).[22]

4. Tolerability

General Adverse Event Profile

• Preliminary reports suggest that rofecoxib 12.5 and 25mg once daily is generally well tolerated in patients with osteoarthritis or acute pain.[13,14,17,19] The most commonly reported adverse events are diarrhoea, headache, nausea and upper respiratory tract infection.[12]

• In comparative trials in patients with osteoarthritis, the overall rate of adverse events with rofecoxib was similar to that observed with ibuprofen 800mg and diclofenac 50mg 3 times daily.[12]

• Currently, no long term data are available concerning the tolerability of rofecoxib. Long term studies with rofecoxib are needed to investigate the effects of prolonged inhibition of constitutive COX-2 in the brain, kidney and other organs.[3,23]

Gastrointestinal Adverse Events

• A combined analysis of 8 clinical trials in patients with osteoarthritis (n = 5435) demonstrated that significantly fewer upper-gastrointestinal perforations, ulcers and bleeds (PUBs) occurred in patients receiving rofecoxib 12.5, 25 or 50mg than in

those receiving ibuprofen 800mg, diclofenac 50mg or nabumetone 500mg three times daily (1.5 vs 2.68%; p = 0.006).[24] The cumulative incidence curve of confirmed and unconfirmed upper-gastrointestinal PUBs over 12 months was also significantly lower with rofecoxib than with the NSAIDs (1.5 *vs* 3.39%; p < 0.001). There were no data presented for the placebo group.

- There was a significantly lower cumulative incidence of gastroduodenal ulceration (≥3mm) with rofecoxib than ibuprofen in 1516 patients (≥50 years of age) with osteoarthritis (p < 0.001) enrolled in 2 studies; the incidence with rofecoxib was similar to that of the placebo group (fig. 3).[25]
- The gastrointestinal effects of rofecoxib in healthy volunteers are reviewed in section 1.

5. Drug Interactions

- Rofecoxib has shown clinically insignificant interactions with rifampin, methotrexate and warfarin.[12] Rifampin 600 mg/day (an inducer of liver metabolism) caused a 50% decrease in plasma concentrations of rofecoxib. Concurrent administration of rofecoxib 75 mg/day (three times the recommended mamximum dose in osteoarthritis) with methotrexate 7.7 to 15 mg/week increased plasma concentrations of methotrexate by 23% and caused an equivalent reduction in its renal clearance. In a 21-day study, prothrombin time (measured as an International Normalised Ratio) increased by 8% in healthy volunteers receiving concurrent warfarin 2 to 8.5 mg/day and rofecoxib 25 mg/day compared with those receiving warfarin.
- In *ex vivo* studies, rofecoxib had no clinically significant effects on the pharmacokinetic and/or pharmacodynamic profiles of ketoconazole, prednisone/prednisolone, oral contraceptives, antacids, cimetidine or digoxin.[12,26-31]
- Rofecoxib had no effect on the cytochrome P450 (CYP) enzyme CYP3A (measured using the erythromycin breath test) in 12 healthy volunteers in a placebo-controlled, double-blind, randomised, crossover trial.[12,28] Also, at concentrations ≤100 μmol/L, rofecoxib reportedly produced no meaningful inhibition of CYP1A2, 2D6, 2E1, 2C9, 2C19, 2E1 and 3A4/5 *in vitro*.[12,28]

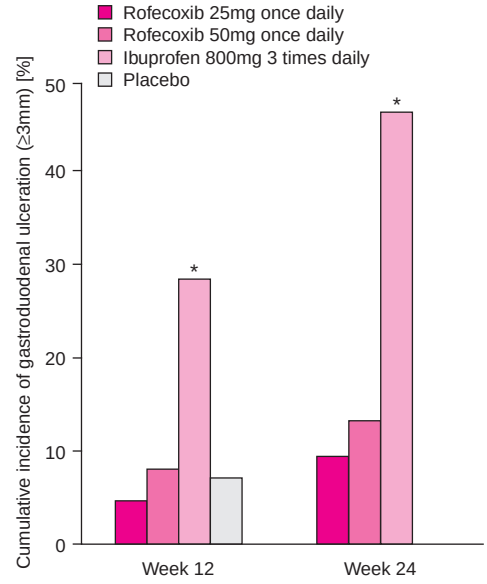


Fig. 3. Comparative cumulative incidence of gastroduodenal ulcers (≥3mm) in 1516 patients with osteoarthritis receiving rofecoxib, ibuprofen or placebo in 2 multicentre, placebo-controlled, double-blind trials.[25] Placebo data were only available at 12 weeks as per study design. *p < 0.001 *vs* rofecoxib.

6. Rofecoxib: Current Status

Rofecoxib, a specific inhibitor of COX-2, is approved for use in patients with osteoarthritis and in adults with acute pain and menstrual pain in the US. The agent effectively relieves symptoms and pain in patients with osteoarthritis and shows analgesic efficacy similar to that of ibuprofen, diclofenac or naproxen sodium. Ongoing phase III trials are investigating its efficacy in rheumatoid arthritis.

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