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Etoricoxib in the 21st Century: An Old Molecule With New Possibilities

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ABSTRACT

Chronic pain conditions, including osteoarthritis (OA), rheumatoid arthritis (RA), ankylosing spondylitis (AS), and acute gouty arthritis (AGA) are responsible for a substantial proportion of global disabilities and healthcare burdens. Etoricoxib, a selective cyclooxygenase-2 (COX) inhibitor, has shown better efficacy in these conditions due to its anti-inflammatory and analgesic properties. Its pharmacokinetic properties allow for rapid absorption and a long half-life, the latter enabling once-daily dosing, which has the impact of enhancing both adherence and symptom relief. Recent pharmacological investigation has evidenced the efficacy etoricoxib intervention in cases of other indications such as dental pain, low back pain (LBP), and postoperative analgesia. Clinical trials and meta-analyses have revealed etoricoxib's superiority over traditional non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen. Novel delivery systems like nanostructured lipid carriers have been proven with to have improved anti-inflammatory effects and decreased cardiotoxicity in preclinical studies. Etoricoxib has shown synergistic outcomes with combination therapies of etoricoxib with tramadol, pregabalin, or thiocolchicoside in the treatment of both acute as well as chronic musculoskeletal pain. This article assembles the latest therapeutic advances and clinical and safety information on etoricoxib, highlighting its emerging role as an important drug in personalized management of pain and inflammation.

KEYWORDS etoricoxib, ankylosing spondylitis, acute gouty arthritis, back pain, osteoarthritis, rheumatoid arthritis, third molar extraction

INTRODUCTION

Pain is a major and growing cause of global morbidity and disability (1). Among the available pharmacological strategies, non-steroidal anti-inflammatory drugs (NSAIDs) remain a backbone for the management of both acute and chronic pain in conditions such as osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis as well as a variety of perioperative and non-arthritic pain syndromes (2). Their clinical usefulness emerges from the inhibition of cyclooxygenase (COX) enzymes, resulting in reduced prostaglandin synthesis and attenuation of inflammatory and nociceptive pathways. Yet the widespread use of conventional, non-selective NSAIDs has been tempered by well-documented gastrointestinal (GI) toxicity, principally ulceration and bleeding due to COX-1 inhibition, and, more recently, by recognition of cardiovascular (CV) risks, particularly in elderly or comorbid populations (3, 4).

To address these safety issues, selective COX-2 inhibitors were designed to retain anti inflammatory activity without damaging the gastric mucosa via COX-1 inhibition (5); however, this inhibition introduced new concerns over cardiovascular

safety, rooted in the prostacyclin-thromboxane imbalance hypothesis. The withdrawal of rofecoxib and valdecoxib underscores the importance of balancing efficacy against the long-term CV risk with this drug class (6). Etoricoxib, marketed since the beginning of the 2000s, is a selective COX-2 inhibitor. With one of the highest COX-2 to COX-1 selectivity ratios among approved agents, it offers potent analgesic and anti-inflammatory effects while maintaining a more favorable GI safety profile compared to non-selective NSAIDs (7, 8). Its pharmacokinetic properties allow for once a day administration because of its rapid absorption and long elimination half life Table 1 (5). The landmark dose finding study determined that 60 mg/day was the dose that provided the optimal balance of efficacy and tolerability in knee osteoarthritis (OA), a key finding that has since been confirmed in numerous randomized controlled trials (9). The strong analgesic and anti inflammatory properties of etoricoxib in OA, rheumatoid arthritis (RA), ankylosing spondylitis (AS), and acute gouty arthritis (AGA), as well as in some non arthritic pain conditions including dental postoperative pain, low back pain (LBP), dysmenorrhea, and preoperative models, have been documented in many investigations, often describing them as effective or better than standard NSAIDs (10-15).

Within the coxib class, etoricoxib's pharmacodynamic and pharmacokinetic characteristics distinguish it from agents like celecoxib, parecoxib, and rofecoxib. While its higher COX-2 selectivity may underpin its stronger anti-inflammatory potency, it also raises cardiovascular safety concerns, particularly in high-risk populations (16, 17). Celecoxib, by contrast, exhibits lower COX-2 selectivity and a different metabolic profile, potentially influencing both its safety and its efficacy balance (18). These distinctions have direct implications for clinical decision-making, especially in complex therapeutic scenarios. This review focuses on etoricoxib analgesic efficacy in various pain conditions and the role of etoricoxib in contemporary clinical practice, whilst also suggesting opportunities for the potential use of etoricoxib in other unique patient groups Figure 1.

Table 1. Pharmacological profile of etoricoxib

Parameter	Details
Mechanism of action	Suppresses prostaglandin synthesis involved in pain and inflammation, with minimal COX-1 effect (19).
Primary indications	Osteoarthritis, rheumatoid arthritis, gouty arthritis, ankylosing spondylitis, acute dental/postoperative pain (20).
Pharmacokinetics	Oral bioavailability ~100%; Tmax: 1-2 hrs; t½: ~22 hrs; hepatic metabolism via CYP3A4; renal excretion as metabolites (21).
Pharmacodynamics	Dose-dependent inhibition of COX-2; spares platelet aggregation and gastric mucosa damage at therapeutic doses (22).
Adverse effects	Cardiovascular risks, edema, rare but serious dermatological reactions, e.g., SJS, TEN (23-25).
Contraindications	Established cardiovascular disease, active peptic ulcer, severe hepatic impairment (26).
Regulatory/clinical status	Approved in multiple countries, restricted/withdrawn in some due to CV safety concerns. Recommended for patients at low CV risk (27).
Formulation and Dosing	Available as oral tablets in dosages of 30, 60, 90, and 120 mg (28)
Fixed-dose combinations approved by DCG	Etoricoxib 10 mg + methyl salicylate 100 mg + menthol 50 mg + linseed oil 30 mg per gm. of gel (for acute musculoskeletal pain), etoricoxib 10 mg + methyl salicylate 20 mg per gm. of cream (acute musculoskeletal pain), etoricoxib + paracetamol (60 mg + 500 mg) tablets (for short term use in acute painful and inflammatory conditions), thiocolchicoside + etoricoxib (4 mg + 60 mg) fc tablets (for the acute treatment of inflammatory musculoskeletal disorders associated with painful muscle spasm in adults), etoricoxib 1%+ menthol 5% spray (for the topical treatment of acute musculoskeletal pain) (29)

COX, cyclooxygenase; Tmax, time to reach maximum plasma concentration; t½, elimination half-life; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; CV, cardiovascular; DCG, drugs controller general; FC, film-coated

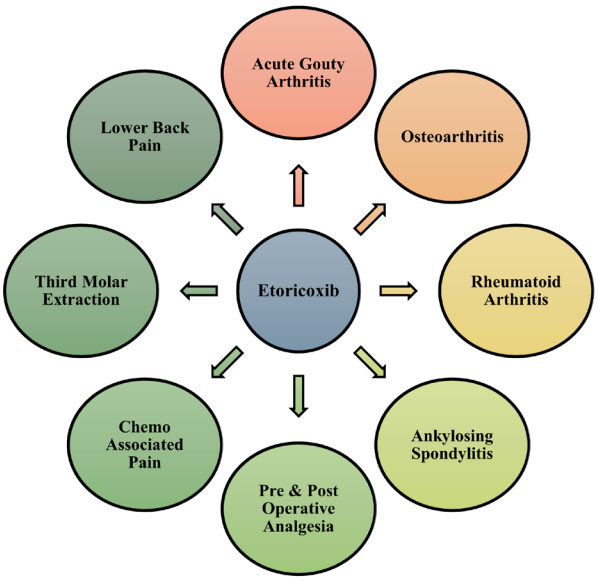

Figure 1. Etoricoxib uses in different pain conditions

ETORICOXIB AND OSTEOARTHRITIS

Etoricoxib is helpful in the symptomatic treatment of OA, a disease in which articular cartilage degenerates and subchondral bone remodulates, leading to inflammation in the synovium (30). OA pathophysiology is characterized by disequilibrium between catabolic and anabolic pathways that result in structural changes (cartilage fibrillation, growth and subchondral sclerosis). With an increasing prevalence due to aging populations and obesity, pain relief and functional improvement are the most urgent goals of OA management, since no disease-modifying treatments have been available until now (31, 32). Guidelines from the American College of Rheumatology (ACR) recommend NSAIDs as the first-line treatment; however, their use is challenged by the GI and CV risk they pose (33-35).

The ability of etoricoxib to selectively target COX-2 results in a more favourable GI safety profile compared with non-selective NSAIDs, which makes etoricoxib a particularly attractive NSAID for use in high-risk patients such as the elderly or patients with a history of GI events (36-39).

In clinical trials, etoricoxib has been shown to be effective at doses of 30-90 mg/day, with 60 mg/day identified as optimal for the relief of pain and improvement of function in knee and hip OA (15, 40-42). Comparative trials, such as the etoricoxib versus diclofenac sodium gastrointestinal tolerability and effectiveness study, have indicated its non-inferiority compared with diclofenac and its superiority compared to ibuprofen in analgesia, with lower GI adverse event (AE) rates (43, 44). Although the rate of discontinuation due to hypertension is higher with etoricoxib, its CV risk profile is similar to that of other NSAIDs, requiring cautious monitoring in high-risk patients (45, 46).

Among the large meta-analyses evaluating the analgesic effect of NSAIDs for OA pain, the 2017 Lancet review ranked etoricoxib amongst the most effective analgesics for OA pain, alongside diclofenac, which has marginal superiority in functional outcomes (47). Rapid onset of action, as early as 4 hours post-dosing, also increases its clinical usefulness. Etoricoxib is recommended as an alternative option to NSAIDs for moderate to severe OA, where topical treatments are unsuitable or GI concerns prohibit the use of non-selective NSAIDs. Although discontinuation is advantageous, this preparation is not without risk in cases of marked renal/hepatic failure (48, 49). Etoricoxib has a good balance of efficacy and tolerability, and provides a strategic therapeutic option for the treatment of OA, although ongoing CV risk assessment is crucial for achieving optimal patient outcomes Table 2.

Table 2. Efficacy and safety of etoricoxib vs other NSAIDs

Comparison area	Etoricoxib efficacy vs traditional NSAIDs
Acute GA	As effective as indomethacin in improving pain and other symptoms (12). Provides an analgesic and anti-inflammatory effect similar to indomethacin, diclofenac, and naproxen (50)
OA	Similar efficacy to naproxen and diclofenac in improving pain and physical function (51) Attenuates OA development and reduces no-ciception in experimental rat models (52)
RA	At least as effective as naproxen (26). One study found etoricoxib to be significantly superior to naproxen for all primary efficacy end-points and clinically relevant response (53)
AS	Effective in patients refractory to other traditional NSAIDs (54)
Acute (postoperative dental)	Superior to acetaminophen/codeine and oxycodone/acetaminophen (55)
GI safety	Better GI safety profile (51), less likely to result in treatment cessation due to NSAID-type GI symptoms (54)
CV safety	Increased risk of CV disorders (hypertension, heart failure, myocardial infarction, stroke) (56, 57). Traditional NSAIDs (e.g., ibuprofen, diclofenac) also carry CV risks (58)
Renal safety	Increased risk of renal adverse effects (48). Traditional NSAIDs also have renovascular effects (e.g., edema, blood pressure elevation, acute renal failure) (59)

GA, gouty arthritis; OA, osteoarthritis; RA, rheumatoid arthritis; AS, ankylosing spondylitis; GI, gastrointestinal; NSAIDs, nonsteroidal anti-inflammatory drugs; CV, cardiovascular

ETORICOXIB AND RHEUMATOID ARTHRITIS

RA, an autoimmune disease with chronic synovial inflammation, joint destruction, and systemic manifestations, can present in either seropositive or seronegative clinical forms (60-63). Recent European Alliance of Associations for Rheumatology (EULAR) recommendations endorse a treat-to-target approach with prompt use of disease-modifying anti-rheumatic drugs (DMARDs), including methotrexate, leflunomide, and sulfasalazine, and short-term glucocorticoids. Additional therapy is required as an adjunct to DMARDs when pain is uncontrolled, with paracetamol followed by NSAIDs.

Etoricoxib stands as a possible alternative in cases of refractory forms of pain (64, 65). Its effectiveness in the treatment of RA has been confirmed in clinical trials (Table 3). In two 12-week randomized trials, etoricoxib at 90 mg/day was superior to placebo and showed similar or greater efficacy than naproxen 500 mg twice daily. All three primary endpoints for tender swollen joint, Patient Global Assessment of Disease Activity, and Investigator Global Assessment showed statistically significant improvements, with higher ACR20 responses for etoricoxib-treated patients compared to naproxen and placebo in the US population. In that study, fast onset and efficacy were observed (21). An 8-week trial determined that 90 mg/day was the optimal dose, with efficacy equivalent to diclofenac (12). Etoricoxib 90 mg/day not only relieves pain but also improves functional outcomes, as measured by improved Health Assessment Questionnaire scores (66). In the light of conflicting transatlantic efficacy findings, the place of etoricoxib in the management of RA is currently that of a useful therapeutic option, especially when traditional NSAIDs are contraindicated or ineffective, in agreement with recommendations aimed at improving quality of life (QoL) in patients with a chronic or incapacitating disorder.

ETORICOXIB AND ANKYLOSING SPONDYLITIS

AS, a chronic inflammatory axial spondyloarthritis, involves sacroiliac joints, facet joints, and spinal ligaments with gradual loss of flexibility and destruction (67, 68). Its pathogenesis includes genetic predisposition (particularly to HLA-B27), immune dysregulation, and environmental factors, is more prevalent in Central Europe and in the male population (69, 70). Clinical findings consist of inflammatory back pain, stiffness, enthesitis, and extra-articular features such as uveitis and idiopathic bowel disorders (71). Current assessments of the Spondylo Arthritis International Society (ASAS) and EULAR guide-

lines emphasize NSAIDs as first-line therapy, advocating chronic use at maximum tolerated doses for symptomatic relief, including inhibition of radiographic progression and reduced CV risk in spondyloarthropathies (72).

Etoricoxib is more effective and better tolerated in the control of AS. In a pivotal 52-week trial, the change in pain with etoricoxib 90 mg/day compared to naproxen 1,000 mg/day was assessed. The design consisted of a 6-week placebo-controlled phase followed by a 46-week active comparator phase. At the end of 6 weeks, etoricoxib exerted a significantly better influence when compared with placebo on the primary end-point parameters such as reduction in spinal pain, improvement in the disease activity, as well as the final Bath Ankylosing Spondylitis Functional Index (BASFI) scores. Etoricoxib was also more effective than naproxen in back pain and disease activity and that superiority was maintained for all 3 domains at 52 weeks. Improvements in ASAS20 were significantly greater, and fewer patients withdrew due to lack of efficacy (73).

A meta-analysis of 26 studies found that more participants achieved pain relief with etoricoxib than with any other NSAID, and that relief was rapid and sustained. Etoricoxib's COX-2 selectivity minimizes side effects, critical for the 5-10% of AS patients with comorbid inflammatory bowel disease (IBD). Data confirmed no increased risk of IBD exacerbation with etoricoxib, bringing the safety profile in line with placebo Table 4 (74).

Cost-effectiveness analyses have shown etoricoxib to be more cost-effective than celecoxib and diclofenac or naproxen, primarily due to lower costs of management of adverse events and improved quality-adjusted life years associated with better Bath Ankylosing Spondylitis Disease Activity Index (BASFI) outcomes (75).

ETORICOXIB AND ACUTE GOUTY ARTHRITIS

Acute gouty arthritis (AGA) is caused by hyperuricemia, which is a serum urate level above saturation of monosodium urate crystal deposits in synovial and periarticular tissues (76-78). In contemporary populations, hyperuricemia is much more common in men than in women (79), leads to gout and also rises dramatically with age (80). Gout clinical presentations include acute and often severe joint pain (especially nocturnal) accompanied by erythema, swelling, and systemic inflammation, and can last for days, resulting in significant functional loss, and frequent emergency hospital visits (81, 82).

Recent ACR and EULAR guidelines recommend a treat-to-target approach centered on achieving pain relief as soon as possible and preventing tissue damage mediated by urate crystals. NSAIDs play a key role in treatment during acute flares and in prophylaxis because of their strong anti inflammatory as well as their analgesic action (83, 84). A systematic review of 22 studies comparing COX 2 selective with non-selective NSAIDs showed that there is no significant difference in effectiveness across drugs, although COX 2 inhibitors have a significantly lower risk of adverse effects. Etoricoxib is as effective as indomethacin, diclofenac, and naproxen in terms of pain relief, inflammation, and safety as it has an improved safety profile, which is crucial since gout patients are often burdened with many comorbid conditions (85).

The efficacy of etoricoxib 120 mg once daily (OD) in the treatment of acute gouty arthritis flares has been demonstrated in two randomized, double blind, comparator-controlled clinical trials. Eligible patients had a recent onset of flare, satisfied the ACR diagnostic criteria, and were experiencing moderate to severe pain. The treatment was for 8 days, with a comparison of etoricoxib 120 mg OD and indomethacin 50 mg three times a day. A greater proportion of etoricoxib-treated patients reported no or mild pain, reflecting the more rapid onset of its analgesic effect relative to indomethacin (86, 87).

On the basis of these findings, the European Medicines Agency has authorized etoricoxib 120 mg OD for AGA (88). Exploratory findings further found significantly more rapid improvement of erythema by 8 days, and post hoc analyses suggest that treatment benefits were due to anti inflammatory and analgesic effects rather than spontaneous improvement. Hence, etoricoxib 120 mg OD is a well tolerated, effective alternative for rapid symptom relief in patients with acute gout which combines the efficacy of conventional NSAIDs with a favourable adverse event profile in patients who are often elderly and frequently comorbid with gout (86, 87).

ETORICOXIB AND RECENT PHARMACOLOGICAL STUDIES

Recent pharmacological studies have demonstrated the pharmacological potential of Etoricoxib in the treatment of several acute and chronic painful conditions. Apart from its uses in traditional conditions, Etoricoxib seems to be a consistent therapeutic option in specific situations such as colonoscopy pain management, taxane- related acute pain syndrome in breast cancer patients, lumbar laminectomy recovery, dental surgeries, LBP, postoperative recovery, and post-bariatric surgery pain. Its selective inhibition of COX-2 produces potent analgesic effects while minimizing the risk of gastrointestinal toxicity typically associated with non-selective NSAIDs (Figure 2).

ETORICOXIB AND DENTAL PAIN MANAGEMENT

Etoricoxib has shown a wide range of analgesic effectiveness in both acute and chronic pain states, in addition to those in arthritis for which it is approved. In pain management in dentistry, it has been postoperatively demonstrated that one dose of oral etoricoxib produces a faster and more pronounced relief than traditional non-selective NSAIDs alone, with better pain scores and patient satisfaction compared with ibuprofen or diclofenac (89, 90). In a study of 56 third molar extraction patients, preoperative administration (120 mg) significantly reduced pain on days 3 and 7, but exerted no difference on inflammation, trismus, or oral health QoL compared with when the drug was given after the surgery (91). In dental implant surgery, etoricoxib was superior to ibuprofen, nimesulide, and acetaminophen in terms of postoperative pain and rescue analgesic consumption (2), and in a different third molar investigation, preemptive administration of etoricoxib resulted in better analgesic and anti inflammatory effects than naproxen (92). Eight high-quality clinical trials are included in a meta-analysis that compared etoricoxib with traditional NSAIDs following third molar surgery. That study reported a strong association between etoricoxib and decreased use of rescue analgesics, and that etoricoxib at 120 mg was the most effective dose, more effective than ibuprofen at 400 mg and sim-

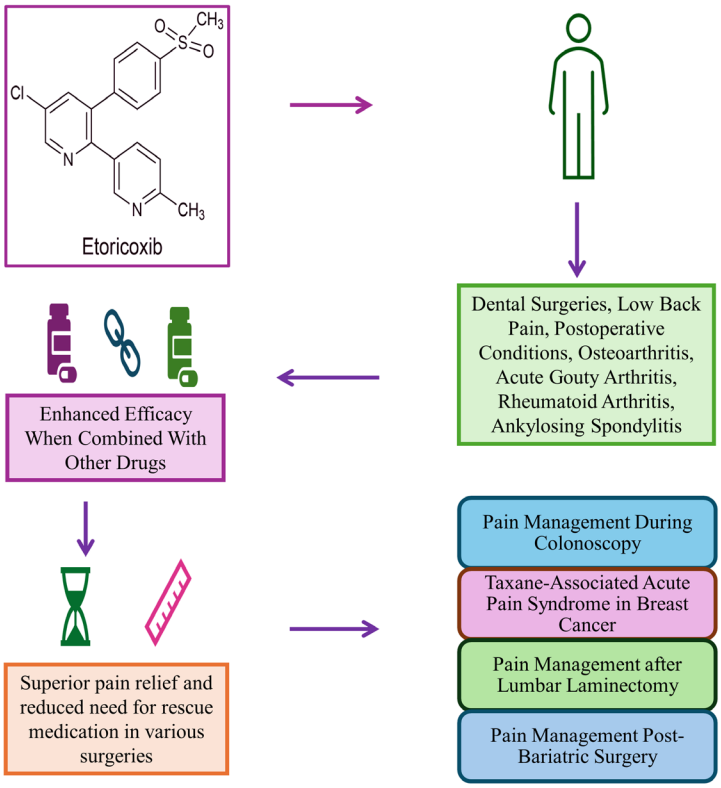

Figure 2. Clinical usefulness and benefits of etoricoxib in pain management and its enhanced efficacy when combined with other drugs

ilar to ibuprofen at 600 mg and naproxen sodium at 550 mg (93).

ETORICOXIB AND LBP

In LBP, 60-90 mg OD of etoricoxib has a stable analgesic effect on pain reduction in both acute and chronic conditions, including spondyloarthritis-associated and axial osteoarthritic back pain (94). In a multimodal Phase III study, fixed-dose etoricoxib/tramadol (90 mg/50 mg) OD was compared with paracetamol/tramadol (975 mg/112.5 mg) thrice daily for 7 days and showed better pain relief on days 3 and 5, a higher proportion of responders by day 3, and similar disability reduction (Oswestry and Roland-Morris scores) and tolerability (95). In chronic LBP, over 21 days etoricoxib 90 mg daily was superior to lornoxicam 8 mg twice daily for pain dimension, allodynia, and central sensitization reduction (96). Real-world data from 383 Indian patients receiving intramuscular etoricoxib (90 mg/mL) confirmed its effectiveness and safety across diverse acute pain scenarios, with clinicians rating it on par with or superior to existing NSAID injections (97).

Preoperative 60 mg dosing also enhanced postoperative QoL in a 60-patient trial (98), while a 39-volunteer trial found that 120 mg etoricoxib significantly reduced both pain and trismus within 48 hours (unlike a placebo), with a short-term benefit on facial swelling comparable to prednisolone (99).

ETORICOXIB AND OPERATIVE ANALGESIA

The preoperative benefit of etoricoxib may also apply to colonoscopy, where 120 mg administered 30 minutes before the procedure significantly reduced pain during cervical biopsy and curettage at both 10 minutes and 24 hours post-procedure without increasing adverse events (100), and in spinal surgery it provided better pain control at 12, 24, and 48 hr after lumbar laminectomy and reduced postoperative morphine consumption (101). But its absorption can be impaired following bariatric surgery due to the change in gastric pH; in this scenario, celecoxib or etodolac can be a better choice (102). In a total knee arthroplasty study, etoricoxib 120 mg/day provided long-acting analgesia, reduced morphine consumption, and had fewer adverse events than both ketoprofen and a placebo (103). A Phase II trial with 144 breast cancer patients revealed that etoricoxib significantly decreased both the incidence and severity of taxane-associated acute pain (104).

ETORICOXIB AND COMBINATION THERAPIES

Combination strategies further heighten etoricoxib's clinical usefulness. In healthy volunteers, a combination of etoricoxib 90 mg and tramadol 50 mg in FDC formulation was the bioequivalent of the combined administration of etoricoxib 90 mg and tramadol 50 mg with a comparable pharmacokinetics and safety profile (105). *In-vitro*, etoricoxib combined with cannabidiol delivered via PLGA nanoparticles on two glioblastoma cell lines, U-138 MG and T98G, the combination significantly reduced cell survival and promoted apoptosis, showing a strong antitumor effect (106).

Etoricoxib-loaded nanostructured lipid carriers (ET-NLCs) significantly reduced radiation-induced cardiac inflammation in rats by enhancing antioxidant activity. The ET-NLCs provided better anti-inflammatory and cardioprotective effects than the plain etoricoxib, indicating that ET-NLCs can be a safer and more potent therapeutic approach (107). Presurgical FDC with etoricoxib 90 mg and dexamethasone 4 mg in third molar extractions enhanced patients' satisfaction, postponed rescue analgesia and decreased swelling (108). In head to head FDC trials, low dose etoricoxib 30 mg plus paracetamol 325 mg showed similar analgesia to ibuprofen/paracetamol, but had a better GI safety profile (109). Etoricoxib 60 mg plus thiocolchicoside 4 mg was better than chlorzoxazone/diclofenac/paracetamol triple FDC in severe LBP (110), and pregabalin/etoricoxib FDC gave greater pain relief, functional improvement, and rescue use reduction than etoricoxib alone in chronic LBP (111). Preoperative etoricoxib in arthroplasty patients showed lower Visual Analogue Scale scores at rest and with activity, and reduced blood loss compared to ibuprofen without an increase in adverse effects (112).

Preclinical studies support that calcium gluconate (50 mg/kg) enhances anti inflammatory activity of low dose etoricoxib (5 mg/kg) in animal models, showing efficacy similar to higher doses of etoricoxib (113); however, comparison of etoricoxib and curcumin against cisplatin induced nephrotoxicity showed that curcumin was

able to provide better protection against oxidative stress and renal dysfunction than etoricoxib, which could only provide marginal benefit (114).

Table 3. Clinical trials findings of etoricoxib

Study	Design	Participants	Intervention	Key findings
IUD insertion pain	RCT, double-blind, placebo-controlled	130 women	Etoricoxib 120 mg vs. placebo	No significant difference in pain scores during/after insertion (115)
MEDAL program (OA/RA CV safety)	Multinational RCTs	34,701 patients	Etoricoxib (60/90 mg) vs. diclofenac 150 mg	CV risk non-inferior (HR 0.96) Fewer GI AEs More hypertension with etoricoxib (116)
Postoperative dental pain	RCT, double-blind	225 patients	Etoricoxib 120 mg vs. oxycodone/acetaminophen	Superior pain relief Longer duration (> 24 h vs. 7.4 h) Less nausea/vomiting (117)
Periodontal surgery (cross-over)	RCT, double-blind	20 patients	Etoricoxib 120 mg vs. dexamethasone 8 mg vs. placebo	Reduced pain vs. placebo 4-8 h post-op (118)
Rheumatoid arthritis (multinational)	RCT, double-blind	891 patients	Etoricoxib 90 mg vs. naproxen 500 mg BID	Similar efficacy to naproxen, fewer GI AEs (66)
Third molar surgery (QoL)	RCT, double-blind	60 patients	Etoricoxib 60 mg pre-op vs. placebo	Lower pain scores Better QoL Less rescue meds (98)
Mandibular surgery	RCT, triple-blind	97 patients	Etoricoxib vs. diclofenac vs. placebo	Superior pain reduction at 2 h/12 h/48 h postoperative (119)
Periodontal surgery (Parallel)	RCT, double-blind	60 taken, 56 completed	Etoricoxib 120 mg vs. celecoxib 200 mg vs. placebo	Lower pain vs. placebo (2-7 h) Fewer rescue meds No pain reduction difference between celecoxib and etoricoxib (120)
Single-implant surgery	RCT, triple-blind	135 patients	Etoricoxib, ibuprofen, nimesulide, and acetaminophen against placebo	Best pain relief from 12 h onward (2)
RA	RCT, double blind	816 patients	Etoricoxib 90 mg, naproxen 500 mg and placebo	Etoricoxib was superior to both placebo and naproxen (121)
Mucogingival surgery	Randomized parallel double-blind	58 patients (out of 60 initially enrolled)	Placebo, 8 mg dexamethasone, and 90 mg etoricoxib	Etoricoxib showed lower pain scores than dexamethasone (122)
Mandibular surgery	RCT	39 volunteers	Etoricoxib 120 mg, prednisolone 10mg, and control group	Etoricoxib showed significant pain reduction and reduction of trismus (99)
Minor oral surgery	RCT, double-blind	40 subjects	Etoricoxib 120 mg and naproxen 500 mg	No difference between etoricoxib and naproxen in decreasing post-extraction pain (92)

Table 3. Clinical trials findings of etoricoxib (continued)

Study	Design	Participants	Intervention	Key findings
RA	RCT, double-blind	761 randomized patients (out of 1014 screened)	Etoricoxib 90 mg, Etoricoxib 10/30/60 mg, placebo	Demonstrated dose-dependent pain improvement with etoricoxib (123)
AS	RCT, double-blind	1015 subjects	Naproxen 1000 mg vs. etoricoxib 60 and 90 mg	Non-inferior pain relief; similar safety (124)
Third molar surgery	RCT, double-blind	56 patients	Etoricoxib 60 mg pre-op vs. placebo	Lower pain (0-12 h) Less rescue use (125)

IUD, intrauterine device; RCT, randomized controlled trial; OA, osteoarthritis; RA, rheumatoid arthritis; AS, ankylosing spondylitis; CV, cardiovascular; HR, hazard ratio; GI, gastrointestinal; AE, adverse event; BID, twice daily; QoL, quality of life; h, hour; mg, milligram

PRECAUTIONS AND ADVERSE EFFECTS

Administration of etoricoxib in specific medical conditions is not recommended due to potential risks. These conditions include active gastrointestinal bleeding or ulceration (126), ischemic heart disease, varying degrees of heart failure (26), peripheral arterial disease, and uncontrolled hypertension consistently exceeding 140/90 mmHg (50). Precautions are suggested for breastfeeding women (127), individuals experiencing central nervous system effects (50), hyperkalemia (128), hypersensitivity reactions (127), NYHA class II-IV congestive heart failure (50), pregnancy (128), severe hepatic dysfunction (50), or severe renal impairment (129).

Table 4. Outcome and findings of meta-analysis studies of etoricoxib

Indication	Key efficacy outcomes	Comparative findings
OA- RCT responder analysis	Higher % achieving > 15-70% pain relief vs. placebo; NNT 3.2-8.9 depending on pain threshold; mean WOMAC pain reduction	No statistically significant differences found in direct comparisons of NNTs among etoricoxib 60 mg and naproxen 1000 mg, etoricoxib 30 mg and celecoxib 200 mg, or etoricoxib 30 mg and ibuprofen 2400 mg (130)
OA - network meta-analysis	Relative efficacy and tolerability based on patient with-drawals due to lack of efficacy or AEs	No significant efficacy/tolerability difference vs. celecoxib or naproxen (131)
Acute gouty arthritis	No significant differences were found in pain relief, tenderness, swelling, or global assessments between etoricoxib and NSAIDs	Etoricoxib 120 mg daily had the same efficacy on acute gout as indometacin and diclofenac. Etoricoxib had a lower incidence of overall adverse events (132)
Laparoscopic cholecystectomy	↓ Pain at 12-24 hrs; reduced analgesic consumption	More effective analgesia without added AEs risk vs. placebo (133)
Third molar surgery	Better analgesia vs. ibuprofen/diclofenac in some trials; fewer rescue analgesics needed	Etoricoxib reduced the number of patients needing rescue analgesics compared to NSAIDs. Adverse effect evaluation showed no statistical difference between etoricoxib and nonselective COX-2 NSAIDs (93)
Postoperative pain after third molar extraction	Lower efficacy treatments (paracetamol 500 and 1,000 mg) showed NNTs that rapidly increased at higher MEC, while high efficacy treatments (ibuprofen plus paracetamol combinations) showed greater separation at higher ME	NNTs for etoricoxib 120 mg were stable. Etoricoxib 120 mg and ibuprofen 200/400 mg plus paracetamol 500/1,000 mg produced the lowest NNTs in the dental pain mode (134)

Table 4. Outcome and findings of meta-analysis studies of etoricoxib (continued)

Indication	Key efficacy outcomes	Comparative findings
Gouty arthritis (acute gout)	No significant differences were detected in pain score change, tenderness, swelling, or patient's/investigator's global assessments between etoricoxib and indometacin	Etoricoxib and indometacin had comparable effects on pain relief. Etoricoxib had a significantly lower risk of overall AEs (135)
Gastrointestinal safety of etoricoxib in OA and RA	Gastrointestinal adverse events (GAEs), defined as events within 28 days after the last dose of study medication	Etoricoxib did not increase the risk of GAEs compared with placebo. Etoricoxib reduced the GAE risk effectively compared with diclofenac and naproxen (136)
CV and GE effects of etoricoxib in OA	Etoricoxib had a significantly lower risk of GI events compared to naproxen	Etoricoxib did not increase the risk of CV events compared to placebo, celecoxib, ibuprofen, or naproxen. The risk of GI events with etoricoxib was comparable to placebo, celecoxib, and ibuprofen (137)

OA, osteoarthritis; RCT, randomized controlled trial; NNT, numbers needed to treat; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; AE, adverse event; NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase; MEC, minimum effective concentration; RA, rheumatoid arthritis; GAE, gastrointestinal adverse event; CV, cardiovascular; GI, gastrointestinal

DISCUSSION

Etoricoxib is a highly selective COX-2 inhibitor designed to provide potent analgesic and anti-inflammatory effects. It has a COX-1/COX-2 IC50 ratio of 344, which is higher than other coxibs:, e.g., celecoxib and valdecoxib (138). This high selectivity means it primarily inhibits COX-2 activity without significantly affecting COX-1 activity. The primary advantage of selective COX-2 inhibitors, including etoricoxib, is their improved GI safety profile compared to non-selective NSAIDs. Pharmacokinetically, etoricoxib is rapidly absorbed, has a long half-life of approximately 20-24 hours, enabling convenient once-daily dosing, and is primarily metabolized by CYP3A4 (139).

Clinically, etoricoxib is approved and effective for a wide range of acute and chronic pain conditions, including osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, acute gouty arthritis, chronic LBP, postoperative dental pain, and primary dysmenorrhea (140). It demonstrates efficacy not inferior or superior to traditional NSAIDs like diclofenac, naproxen, and ibuprofen across these indications, often with a faster onset in acute settings like dental pain (43, 44). Combination therapies, such as fixed-dose combinations with tramadol, pregabalin, or paracetamol, enhance analgesia and reduce rescue medication needs in musculoskeletal and postoperative pain (105, 111, 134). Novel delivery systems like etoricoxib-loaded nanostructured lipid carriers (NLCs) show promise for enhanced anti- inflammatory and potential cardioprotective effects in preclinical models (107).

Clinical trials (Table 3) and meta-analysis (Table 4) indicate that etoricoxib provides effective analgesia for osteoarthritis, acute gout, and postoperative pain, with efficacy generally comparable to other NSAIDs and COX-2 inhibitors. It often shows a gastrointestinal safety advantage over traditional NSAIDs and does not appear to elevate cardiovascular risk relative to placebo or common comparators. In acute gout, its tolerability profile is more favorable, with fewer adverse events than indometacin or diclofenac (135).

CONCLUSIONS

Etoricoxib continues to hold significant clinical value as a selective COX-2 inhibitor, offering potent and sustained analgesic effects across diverse pain conditions. Its demonstrated efficacy in chronic inflammatory diseases such as osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis, as well as acute conditions like gout and dental pain, reinforces its utility in both primary care and specialized settings. Importantly, its favorable gastrointestinal safety profile compared to traditional NSAIDs makes it a preferred

option in patients at higher risk for GI complications. Emerging formulations and combination therapies, such as those with tramadol or pregabalin, have further enhanced its therapeutic range, allowing for more personalized and tolerable pain management strategies.

Despite its established role in pain control, several avenues remain open for expanding the pharmacological and clinical applications of etoricoxib. Future investigations should explore its potential as part of disease-modifying protocols, particularly in chronic inflammatory states where structural progression is a concern. The development of advanced drug delivery systems, including nanocarriers and targeted-release formulations, may improve site-specific action and reduce systemic exposure. Moreover, the safety and efficacy of etoricoxib in underexplored contexts, such as cancer-related or neuropathic pain, warrant rigorous clinical trials. Integrating pharmacogenomic data could also refine patient selection and optimize risk-benefit outcomes in long-term use.

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CONFLICTS OF INTEREST

The author's state no conflicts of interest related to this investigation.

AUTHOR CONTRIBUTIONS

M.A.A.: conceptualization, methodology, software, writing & editing; data curation, writing-original draft preparation, visualization, investigation; A.K.: data curation, writing- original draft preparation; supervision, project administration, review; validation, formal analysis, resources.

All authors have read and agreed to the published version of the manuscript.

DATA AVAILABILITY STATEMENT

All data used in this review were obtained from prior publications and are openly accessible through the referenced literature, ensuring the transparency of the discussion.

INSTITUTIONAL REVIEW BOARD STATEMENT

This review article does not present any new experimental research involving humans or animals, and therefore ethics approval was not necessary.

INFORMED CONSENT STATEMENT

This review did not include studies involving human subjects, so informed consent was not required.

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