Update on the clinical pharmacology of etoricoxib, a potent cyclooxygenase-2 inhibitor

Alejandro Escudero-Contreras, Janitzia Vazquez-Mellado Cervantes & Eduardo Collantes-Estevez†

†*Author for correspondence*
"Reina Sofia" Univerity Hospital", Department of Rheumatology, Avda. Menendez Pidal s/n, 14004 Córdoba, Spain
Tel.: +34 957 011 631;
Fax: +34 957 011 683;
eduardo.collantes.sspa@juntadeandalucia.es

A review of the literature on etoricoxib, a highly selective cyclooxygenase (COX)-2 inhibitor, or coxib, which has been approved in 62 countries, was undertaken by the authors. Etoricoxib is an effective analgesic drug that has shown advantages over traditional nonsteroid anti-inflammatory drugs. These advantages include a lower incidence of gastrointestinal adverse events, a similar thrombotic cardiovascular risk profile, rapid action, 27-h effect, sustained long-term effects and effectiveness in the treatment of gouty arthritis, rheumatoid arthritis, ankylosing spondylitis and osteoarthritis. The recently concluded Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program compared etoricoxib with the most widely used NSAID in the world, diclofenac, in almost 35,000 patients with osteoarthritis and rheumatoid arthritis under clinical practice conditions. This study confirmed a similar incidence of cardiovascular thrombotic events and renal dysfunction, a higher incidence of edema and hypertension, and a lower incidence of gastrointestinal and hepatic adverse events in etoricoxib versus diclofenac. Etoricoxib is an appropriate choice for the treatment of osteoarthritis and rheumatoid arthritis and for the relief of gouty pain in patients with low cardiovascular risk but an increased risk of gastrointestinal complications.

Keywords: acute gouty arthritis, acute pain, ankylosing spondylitis, cardiovascular toxicity, chronic low-back pain, chronic musculoskeletal pain, COX-2, coxibs, etoricoxib, gastrointestinal toxicity, nonsteroidal anti-inflammatory drugs, osteoarthritis, post-extraction dental pain, primary dysmenorrhea, renal toxicity, rheumatoid arthritis

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Nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of compounds that act by inhibiting prostanoid biosynthesis and have been widely prescribed for decades for the treatment of pain, fever and inflammatory disease [1]. In 2003, antirheumatic NSAIDs were responsible for 3% of all drug sales in the world, with an annual growth rate of 6%.

The traditional limitation of NSAID use has been unwanted side-effects (primarily gastrointestinal [GI] and renal toxicity), which are also generally dependent on the inhibition of prostanoid biosynthesis [2–4]. Two isoforms of prostaglandin (PG)-G/H synthase mediate prostanoid biosynthesis: cyclooxygenase (COX)-1 and -2. COX-1 is involved in GI effects and COX-2 in inflammatory action. Consequently, COX-2 has long been a target for the development of inhibitory molecules that can provide anti-inflammatory benefits without GI side effects. Etoricoxib is one of the latest COX-2-selective inhibitors developed in the course of a long search for effective substances that are free of side effects and suitable for use in patients who are generally older and have chronic painful rheumatic conditions that limit mobility and curtail quality of life.

Role of prostanoids in health & diseases

Prostanoids are ubiquitous lipid mediators that modulate a wide variety of physiologic and pathologic processes [5]. Prostanoids are formed from arachidonic acid (AA), which is released from membrane phospholipids by phospholipase A2 and then transformed by PG-G/H synthase into PG-G2 and then into the unstable endoperoxide PGH2. The resulting prostanoids, including PGE2, PGF2α, PGD2, prostacyclin (PGI2) and thromboxane (TX)A2, are molecules that intervene in many cellular responses and pathophysiologic processes, such as: modulation of the inflammatory reaction, erosion of cartilage and juxta-articular bone, GI cytoprotection and ulceration, angiogenesis and cancer, homeostasis and thrombosis, renal hemodynamics and progression of kidney disease. TXA2 is a potent vasoconstrictor and stimulator of platelet aggregation; PGI2 is expressed in the vascular endothelium and inhibits platelet aggregation; and PGE2 and PGI2 are powerful vasodilators that increase blood flow to inflamed areas [6]. The vasodilatory properties of PGE2 and PGI2 help to enhance gastric mucus secretion, thus reducing acidity and pepsin content in the stomach and protecting the integrity of the gastric mucosa [7]. In the kidney, PGE2 and PGI2 increase blood flow in response to vasoconstrictive factors and help to modulate glomerular filtration rate in the event of volume depletion [2,7–10].

The PGH-synthase (PGHS) isoforms, COX-1 and -2, also known as PGHS-1 and -2, have been cloned and characterized [8,11].

Regulation of isoenzyme expression differs between the two isoforms [9,10,12]: COX-1 is encoded by a 'housekeeping gene' and is constitutively expressed in virtually all tissues, whereas the gene for COX-2 is a primary response gene with many regulatory sites. It has been postulated that while COX-1 is constitutive and expressed in mammalian cells, particularly endothelium, platelets, GI mucosa (where it orchestrates submucosal blood flow) and kidneys in physiologic conditions, COX-2 is induced in pathological conditions by inflammatory stimulation [7,13,14]. The original hypoyhesis was that COX-1 is constitutive and is involved in homeostatic processes, whereas COX-2 plays a major part in the inflammatory process and associated pain. However, whilst the mRNA for COX-2 is found in many tissues of the body, COX-2 is not normally present as a functionally active enzyme. Enzyme activation requires induction or upregulation by cytokines, growth factors and mitogens [2,10]. Evidence is accumulating to suggest that the actions of COX-1 and -2 overlap and that both isoforms intervene in homeostatic processes and the modulation of inflammatory reactions.

Recent findings in human studies show that COX-2 is expressed constitutively in many organs, particularly the CNS [15], reproductive tissues [16] and kidney [17–19]. The kidney shows abundant expression of both isoenzymes, with COX-1 expressed primarily in the vascular smooth muscle and collecting ducts of the kidneys and COX-2 expressed predominantly in the macula densa, interstitial cells of the medulla and cortical thick ascending limb [20]. While COX-1 expression does not translate into dynamic regulation, COX-2-derived prostanoids mediate renin release in the macula densa and are involved in the tubular control of sodium, potassium and water excretion [21]. Renal COX-2 activity leads to the synthesis of renal PGI2 and PGE2, which have been shown to influence vascular homeostasis, the regulation of normal blood flow and glomerular filtration rate [17].

However, investigators have naturally been aware that one theoretical problem of selective COX-2 blockade is that any reduction in PGI2 synthesis might leave TXA2 production unchecked [22], potentially favoring vasoconstriction and stimulation of platelet aggregation [23]. Blockade of the strong platelet aggregation inhibitor PGI2 could increase thrombotic risk [24,25]. PGI2 and TXA2 are vital for the normal functioning of the cardiovascular (CV) system, so the CV thrombotic effects of COX-2 inhibitors have been closely scrutinized since this line of investigation was opened. One result of the intensive study of COX-1 and -2 is the concept that these enzymes have mutually exclusive functions – this is oversimplified and needs to be revised [7].

COXIBs versus conventional NSAIDS

In 1971, Vane demonstrated that the anti-inflammatory action of NSAIDs depends on their ability to inhibit the activity of the enzyme COX [1], which reduced the synthesis of proinflammatory PGs [26]. Traditional nonselective NSAIDs inhibit both COX-1 and -2 at therapeutic doses [27], deriving their therapeutic utility from their COX-2 inhibition and their GI toxicity from COX-1 inhibition [28]. Since COX was shown to have two distinct isoforms [26,29], several new agents have been developed to selectively inhibit COX-2 activity with the aim of obtaining products as effective as nonselective NSAIDs without the GI tolerability concerns associated with COX-1 inhibition. Consistent with this expectation, available COX-2-selective NSAIDs have an efficacy similar to conventional NSAIDs, but have better GI tolerability in the treatment of rheumatoid arthritis (RA), osteoarthritis (OA) and acute pain [30].

Recent evidence that treatment with COX-2-selective NSAIDs have been associated with an increased risk of CV events compared with placebo and the suggestion from observational studies and a meta-analysis of randomized clinical trials of possible differences among traditional NSAIDs with respect to CV risk, raise the clinical issue of what differential risk might exist between COX-2-selective and traditional NSAIDs [31–33].

The intense focus on the coxibs as a result of potential CV thrombotic problems also revealed that the CV risks of nonselective NSAIDs may not have been fully evaluated. The issue of CV thrombotic complications is likely to be more complex than COX-2 selectivity itself and levels of COX-2 selectivity, including what constitutes CV risk in the absence of heart attack or stroke, the role of disease-specific factors, age, and other population-specific factors

Etoricoxib

Etoricoxib was introduced into clinical practice in 2002 and was approved by the European

Medicines Agency (EMEA) for acute and chronic treatment of the signs and symptoms of OA and RA, treatment of ankylosing spondylitis (AS), treatment of acute gouty arthritis, relief of acute and chronic pain, and treatment of primary dysmenorrheal. Here we will review all the relevant pharmacologic issues related to etoricoxib.

Chemistry

Etoricoxib is a novel bipyridine COX-2 selective inhibitor (Figure 1) [34,35]. In contrast with celecoxib, valdecoxib and parecoxib (Figure 1B), etoricoxib is a methylsulfone (Figure 1A) and does not contain the sulfonamide moiety that has been associated with an increased risk of hypersensitivity reactions.

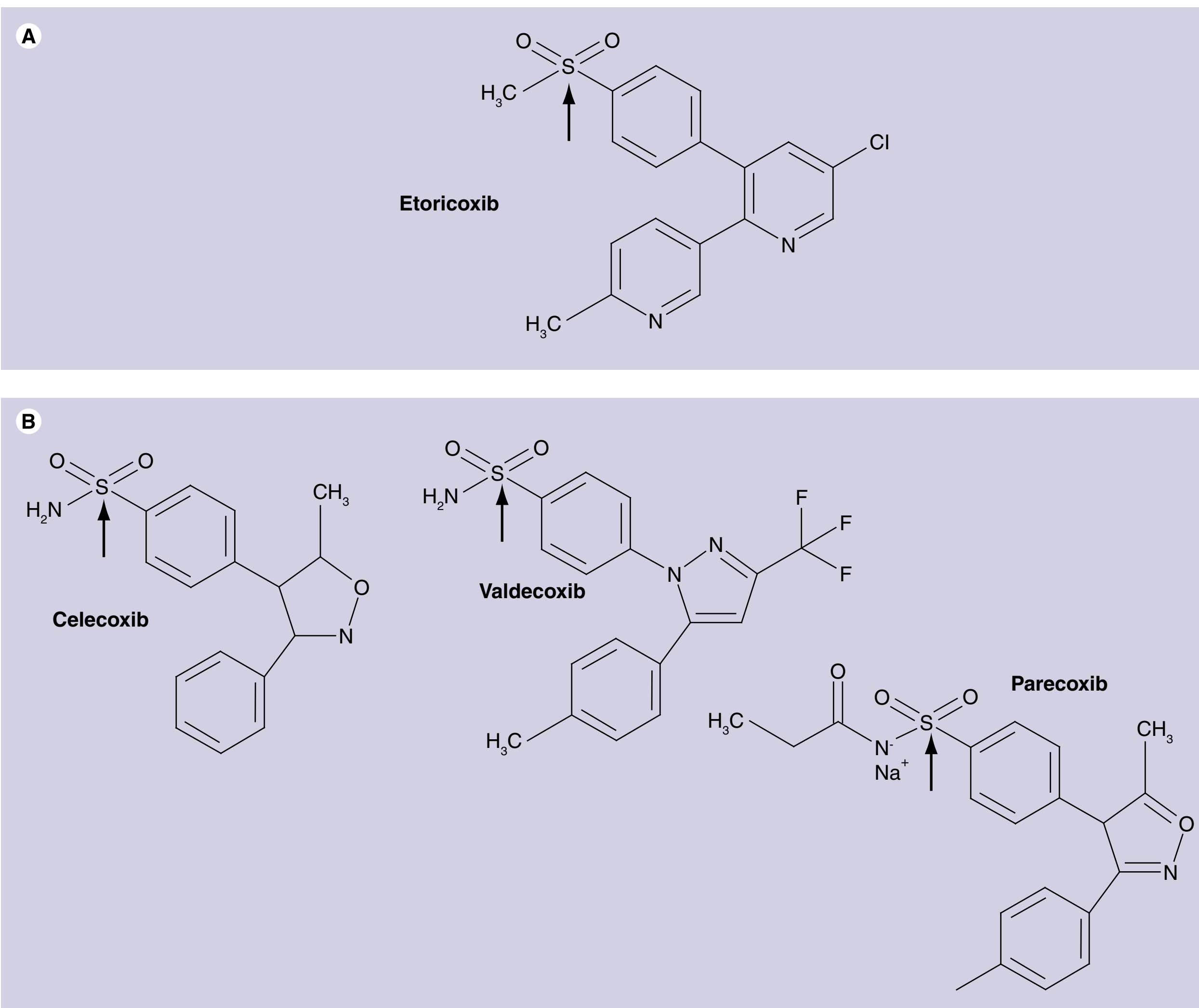
Pharmacodynamics

Etoricoxib is highly selective for the COX-2 enzyme. It is 100-fold more selective for COX-2 than COX-1 and it appears to have little interaction with COX-1 (Table 1) [36].

Selectivity is a measure of the drug concentration required to inhibit each PG-synthase isozyme activity by 50%, commonly expressed as the COX-1/COX-2 IC_{50} ratio [2,37], and the concept has been applied to *in vitro* studies made during drug screening [2,38].

In human whole blood assays, etoricoxib has a COX-1/COX-2 IC_{50} ratio of 344 ± 48 [38–40]. Capone and colleagues found that etoricoxib reduces platelet COX-1 and monocyte COX-2 activity, with IC_{50} values of 162 ± 12 µM (mean ± standard error) and 0.47 ± 0.06 µM,

Figure 1. Etoricoxib, celecoxib, valdecoxib and parecoxib.



Note that the arrow heads show the methylsulfone moiety contained in etoricoxib. The structures in panel B are sulfamides.

Table 1. Pharmacokinetic characteristics of etoricoxib.

Chemistry	Sulfonyl derivative
COX-1/COX-2 IC_{50} ratio *in vitro*	344
Pharmacokinetics	
Oral bioavailability (%)	100
Time to maximal plasma concentration (h)	1
Maximal plasma concentration (ng/ml)*	788
Half-life (h)	27
Volume dist. (l)	120
Bound in plasma (%)	92
Metabolism	
Main pathway of liver metabolism	Oxidation by cytochrome P-450 (3A4)
Urinary excretion (%)	70
Approved daily doses (mg)	
For osteoarthritis	60
For rheumatoid arthritis	90
For acute gouty arthritis	120
For acute pain and primary dysmenorrhea	Up to 120
Chronic low-back pain	Up to 90
Familial adenomatous polyposis	Not approved

**After the administration of 40 mg.*

respectively [41]. After lumiracoxib, etoricoxib is the second most selective COX-2 inhibiting drug [42].

The administration of single doses of etoricoxib (5–500 mg) is associated with dose- and time-dependent inhibition of whole blood COX-2 activity *ex vivo* without significantly affecting platelet COX-1 activity [39,43]. Maximal COX-2 inhibition occurs in 1.5 h and recovers slowly. Repeated oral dosing of etoricoxib during 9 consecutive days (25–150 mg once daily) caused a dose-dependent inhibition of monocyte COX-2, but not platelet COX-1 [39,44]. Monocyte COX-2 activity was reduced by 82 and 93%, respectively, and then recovered slowly (4 h after the last dose of etoricoxib 100 and 150 mg was administered). In fact, profound inhibition is still present at 24 h (60 and 80%, respectively), which is the basis for the convenient once-daily dosing regimen of etoricoxib. In a study of the effect of etoricoxib (120 mg once daily) versus naproxen (500 mg twice daily), administered for 4 consecutive days, on PGE2 synthesis in gastric biopsies of healthy subjects, naproxen significantly inhibited gastric PGE2 synthesis but etoricoxib did not [45]. These results suggest that etoricoxib meets criteria for specific COX-2 inhibition at therapeutic dosing.

Pharmacokinetics & metabolism

Etoricoxib is well absorbed from the GI tract after oral doses. Rodrigues *et al.* demonstrated an average absolute bioavailability of 83% (range: 70–99%) after an oral dose administered as a solution in polyethylene glycol-400 [46]. This oral bioavailability is somewhat lower than that reported by Agrawal *et al.* for tablet formulations (average: 100%; range: 93–100%) [43].

Peak plasma concentrations are reached in approximately 1 h (C_{max}: 1.36 µg/ml; T_{max}: 1 h) and plasma protein binding is approximately 92%. Systemic etoricoxib clearance is relatively low (49 ml/min) and the steady-state volume of distribution is large (120 l) resulting in a relatively long terminal half-life ($T_{1/2}$) of approximately 27 h [43].

The mean area under the plasma concentration-time curve (AUC) is 37.8 mgh/l [30]. A high-fat meal can affect the rate, but not the extent, of absorption of a 120-mg tablet of etoricoxib [36]. AUC remains unaffected, as might be expected given the 100% bioavailability of etoricoxib [43], whereas C_{max} is 36% lower and appears 2 h later when the drug is administered after a high-fat meal [36,43]. Etoricoxib can therefore be administered without concern for food intake [34] because any variations due to food intake are not expected to have clinical significance [30,43].

The drug displays linear pharmacokinetics up to at least twice the highest recommended daily dose of 120 mg [43]. Etoricoxib is extensively metabolized in humans (>90% of dose) with less than 1% of a dose recovered in urine as the parent drug [34]. Etoricoxib undergoes P450-dependent oxidation and 6′-methyl hydroxylation is the major metabolic pathway in human liver microsomes. The CYP3A subfamily, most likely CYP3A4, are the principal human liver microsomal enzymes involved in etoricoxib hydroxylation [47]. The 6′-hydroxymethyl derivative of etoricoxib is then oxidized to the 6′-carboxylic acid derivative (the major metabolite) by CYP3A4. Both metabolites are inactive or only weak COX-2 inhibitors. Although CYP3A4 accounts for 40–90% (mean: 68%) of total 6′-methyl hydroxylase activity in human liver microsomes, the remainder of the activity is divided equally among a number of other P450s (e.g., CYP2D6, CYP2C9, CYP1A2, and, possibly, CYP2C19) [47].

The P450 reaction phenotype of etoricoxib differs from that of other COX inhibitors. Celecoxib, valdecoxib, meloxicam, lornoxicam, ibuprofen, flurbiprofen and indomethacin are metabolized extensively *in vivo*, primarily (80%)

by a single P450 form (CYP2C9) in human liver microsomes [48]. Hepatic insufficiency tends to decrease systemic clearance of these molecules and impair drug elimination. However, hepatic insufficiency has no effect on the absorption, plasma protein binding or distribution of etoricoxib. The recommended dose of etoricoxib in patients with mild hepatic impairment is 60 mg once daily; patients with moderate impairment should be given 60 mg every other day. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency, so etoricoxib is not recommended for these patients [49].

Excretion is mainly urinary (70%), with only 20% of a dose appearing in feces. Less than 1% of an oral dose of etoricoxib is recovered intact in urine 24 h post-dose, so renal insufficiency would not be expected to have any direct effect on drug elimination. Two studies have demonstrated that renal impairment has no clinical meaningful effect on the pharmacokinetics of etoricoxib [50]. Parameters such as AUC, C_{max}, T_{max}, $T_{1/2}$ and plasma protein binding are not affected in a clinically important way in patients with impaired renal function compared with healthy subjects. Likewise, hemodialysis has no significant effect on the pharmacokinetics of etoricoxib in patients with end-stage renal disease. These findings indicate that no dosing adjustments are necessary for patients with renal impairment. However, patients with advanced renal disease (creatinine clearance <30 ml/min) are likely to be very sensitive to any further deterioration of renal function and there is no long-term clinical experience in these patients. Consequently, the use of etoricoxib is not recommended in subjects with advanced renal disease [50].

Interactions with other drugs

Etoricoxib does not significantly inhibit or induce CYP3A4 *in vitro* so it is unlikely to affect the pharmacokinetics of other drugs metabolized by CYP3A4 [30,47]. Etoricoxib does not have clinically important effects on the pharmacokinetics of prednisone or prednisolone, and antacids or ketoconazole have no clinically important effects on the pharmacokinetics of etoricoxib. By contrast, etoricoxib may influence the plasma pharmacokinetics of oral contraceptives, oral anticoagulants, digoxin and methotrexate [30,34,48].

Oral contraceptives

Coadministration of etoricoxib 120 mg and an oral contraceptive containing ethinylestradiol 35 µg/norethindrone 0.5–1 mg for 21 days, either concomitantly or separated by 12 h, increased the steady-state $AUC_{0-24\,h}$ of ethinylestradiol by 50–60%, whereas norethindrone concentrations generally did not increase in a clinically relevant way.

Warfarin

Administration of etoricoxib 120 mg once daily in patients receiving long-term warfarin therapy is associated with a 13% increase in the international normalized ratio (INR). Thus, patients receiving warfarin and etoricoxib should have their INR closely monitored, especially after etoricoxib therapy is started or the etoricoxib dosage is changed [51].

Digoxin

Etoricoxib 120 mg once daily administered for 10 days to healthy volunteers causes an increase in digoxin C_{max} of approximately 33%, but this increase is not generally important for most patients. However, patients considered at high risk of digoxin toxicity should be monitored when these drugs are coadministered.

Methotrexate

In two studies, administration of etoricoxib 60 or 90 mg once-daily for 7 days (recommended doses for the treatment of chronic conditions such as OA and RA) did not alter the AUC or renal clearance of methotrexate in patients with RA receiving methotrexate 7.5–20 mg once weekly. Similarly, etoricoxib 120 mg once-daily did not affect the AUC or renal clearance of methotrexate in one of the studies, but in the second study, administration of etoricoxib 120 mg once daily was associated with a 28% increase in methotrexate AUC and a 13% reduction in methotrexate renal clearance. Thus, patients receiving both drugs should be properly monitored for methotrexate-associated toxicity.

Angiotensin-converting enzyme inhibitors & furosemide

As with nonselective NSAIDs and other coxibs, the potential interaction of etoricoxib with angiotensin-converting enzyme (ACE) inhibitors and furosemide should be considered [34]. The mechanism(s) of NSAID-related hypertension is/are unclear. COX-2-derived prostanoids mediate renin release in the macula densa and are involved in the tubular control of sodium, potassium and water excretion [21]. Although all NSAIDs interfere with essentially all antihypertensive drugs, the rank ordering is ACE inhibitor/angiotensin receptor blockers > diuretic > β-blocker >> calcium antagonist or α-blocker. Most authorities recommend that NSAIDs be discontinued or used only occasionally in hypertensive patients [52].

Rifampicin

Etoricoxib coadministered with rifampicin, a potent inducer of hepatic metabolism, produces a 65% decrease in etoricoxib plasma AUC [30,34]. Also, rifampicin may enhance the nephrotoxic effects of cyclosporine or raise tacrolimus and lithium plasma levels. Therefore, renal function and blood lithium should be monitored when etoricoxib is combined with either of these drugs [53].

Acetylsalicylic acid

The potential interference of etoricoxib with the irreversible inactivation of platelet COX-1 by aspirin has been studied recently in a double-blind, randomized, placebo-controlled trial. In healthy subjects, steady-state plasma concentrations of etoricoxib (120 mg daily for 12 consecutive days) did not affect the inhibitory effects of aspirin (81 mg administered daily during 6 days) on *ex vivo* TXB2 production during whole blood clotting and platelet aggregation in response to acetylsalicylic acid (1.6 mM) or collagen (1 µg/ml) [39]. Etoricoxib, unlike some traditional NSAIDs such as ibuprofen and naproxen does not interfere with the antiplatelet effect of low-dose aspirin [54,55]. Last year, the FDA recommended that patients taking aspirin avoid concomitant ibuprofen use due to interaction effects [201].

Clinical efficacy

A number of randomized clinical trials have evaluated etoricoxib in distinct indications: OA, RA, acute gouty arthritis, acute pain (postoperative dental pain and primary dysmenorrhea), chronic low-back pain and ankylosing spondylitis (**Tables 2–5**).

Osteoarthritis

The published reports from the Phase IIb/III clinical trials conducted for registration purposes showed that etoricoxib provides clinical meaningful benefit to patients with OA as well as RA [56–58]. Maximal efficacy in OA with etoricoxib was achieved with a dose of 60 mg once daily.

Zacher *et al.* compared the efficacy, safety and tolerability of etoricoxib 60 mg once daily (n = 256) in a 6-week, double-blind, parallel-group study to the active comparator diclofenac 50 mg three-times daily (n = 260) [59]. The study was conducted in 67 centers of 29 countries (not the USA). Use of rescue medication (acetaminophen) was allowed and recorded.

Low-dose etoricoxib (60 mg once daily) exhibited an efficacy similar to that of high-dose diclofenac (150 mg daily) on all end points except early efficacy, in which etoricoxib demonstrated significantly greater benefit with 4 h of taking the first dose on the first day of therapy ($p = 0.007$), as evaluated by the percentage of patients with good or excellent response (patient global assessment of response to therapy). Treatment effects were similar by day 2 and sustained throughout 6 weeks of therapy. The maximum treatment effect was evident at week 2 and persisted at a similar level for the remainder of the study.

Etoricoxib and diclofenac had a generally favorable safety profile and were well tolerated over the 6-week treatment period. Discontinuations due to drug-related adverse experiences were 3.5% with etoricoxib and 3.1% with diclofenac. The only significant difference ($p > 0.025$) in adverse effects was for drug-related abnormal laboratory values, which were more common in the diclofenac group. The most common drug-related adverse experiences in both groups were GI disorders (etoricoxib 12.9% vs diclofenac 14.2%) and general disorders and administration site conditions (etoricoxib 4.7% vs diclofenac 4.6%). Peripheral edema, hypertension, angina pectoris and congestive heart failure (CHF) occurred in 0–3.5% of patients, always more frequently in the diclofenac group, but the difference was not significant.

Curtis *et al.* studied the long-term efficacy and tolerability of etoricoxib in 617 patients with OA of the knee in 55 centers in the USA [60]. In Part I (6 weeks), patients were allocated to once-daily oral etoricoxib 5, 10, 30, 60, 90 mg or placebo. In Part II (8 weeks, 550 patients), the placebo, etoricoxib 5 and 10 mg groups were reallocated to etoricoxib 30, 60 or 90 mg once daily or diclofenac three-times daily. Treatment was continued for consecutive 12-week (427 patients) and 26-week extensions.

The etoricoxib groups displayed significant ($p < 0.05$), dose-dependent efficacy for all primary end points in Part I. In Part II, the efficacy of etoricoxib was maintained throughout the 52 weeks of the study with good tolerance; efficacy was similar to that of diclofenac. Both etoricoxib and diclofenac produced an improvement of clinical importance (10 mm on the VAS Western Ontario and McMaster's University Osteoarthritis Index [WOMAC] Pain Subscale or

Table 2. Clinical efficacy of etoricoxib in osteoarthritis.

Primary end point	Treatments	Results	Ref.
Osteoarthritis of knee			
Pain on walking, assessed using the VAS 100 mm (question one of WOMAC), patient global assessment of response to therapy (PGART) (five-point Likert scale, from 0 = excellent to 4 = none) and investigator global assessment of disease status	Part I. Etoricoxib 5, 10, 30, 60 or 90 mg o.d. versus placebo for 6 weeks. Part II. Etoricoxib 30, 60 or 90 mg o.d. versus diclofenac (50 mg t.i.d.) for 8 weeks.	Part I. At 6 weeks, for all three primary end points, each etoricoxib treatment group showed significant greater efficacy versus placebo. Maximal efficacy was seen with 60 mg Part II. etoricoxib 30, 60 and 90 mg were generally similar to diclofenac 150 mg o.d. The clinical efficacy of etoricoxib was sustained over 14 weeks	[56] [60]
Osteoarthritis of knee or hip			
WOMAC pain and physical function subscales 100 mm VAS and patient's global assessment of disease status	60 mg o.d. versus placebo versus naproxen 500 mg b.i.d. for 12-weeks	60 mg o.d. versus placebo versus naproxen 500 mg b.i.d. for 12 weeks	[57]
	Etoricoxib 30 mg o.d. versus ibuprofen 800 mg t.i.d. versus placebo	Etoricoxib and ibuprofen were statistically superior to placebo for all end points	[58]
	Etoricoxib 60 mg o.d. versus placebo or diclofenac 50 mg t.i.d for 6-weeks	Etoricoxib is clinically effective in the therapy of osteoarthritis, providing a magnitude of effect comparable to that of the maximum recommended daily dose of diclofenac. The onset of clinical benefit with etoricoxib on day one is more rapid than that of diclofenac	[59]
Osteoarthritis of knee or hip			
WOMAC pain and physical function subscales 100 mm VAS and patient's global assessment of disease status	Part I. Etoricoxib 60 mg o.d. versus naproxen 500 mg b.i.d. versus placebo for 12 weeks. Part II. 40 weeks. Placebo group were changed to etoricoxib or naproxen. Extension of 86 weeks	Etoricoxib and naproxen have demonstrated significantly greater improvement versus placebo in all WOMAC end points The onset of clinical benefit were observed at week 2 All groups had the same percentage of AE	[61]
	Etoricoxib 30 mg daily versus ibuprofen 800 mg t.i.d. versus placebo during 12 weeks	Etoricoxib and ibuprofen were statistically superior to placebo for all end points	[62]
	Part I. Etoricoxib 30 mg o.d. versus celecoxib 200 mg o.d. versus placebo for 12 weeks. Part II. Placebo groups were distributed to etoricoxib or celecoxib groups for 14 weeks.	Etoricoxib is at least as effective as celecoxib 200 mg o.d. and superior to placebo group in all end points The safety of both group were similar	[63]

b.i.d.: Twice daily; o.d.: Once daily; t.i.d.: Three-times daily, WOMAC: Western Ontario McMasters Universities Osteoarthritis Index.

Table 3. Clinical efficacy of etoricoxib in rheumatoid arthritis and acute gouty arthritis.

Primary end point	Treatments	Results	Ref.
Rheumatoid arthritis			
Patient global assessment of disease activity (10-mm VAS), investigator global assessment of disease activity (Likert scale), tender joint count and swollen joint count	Etoricoxib 90 mg o.d. versus naproxen 500 mg b.i.d. versus placebo for 12 weeks	For all primary end points, etoricoxib and naproxen were statistically superior to placebo or similar to naproxen	[64]
		Etoricoxib was significantly superior to naproxen and placebo in all of primary end points	[65]
Acute gouty arthritis			
Patients' assessment of pain in the study joint (0–4 point Likert scale) over days 2–5	Etoricoxib 120 mg o.d. versus indomethacin 50 mg t.i.d. for 8 days	Both treatment groups experienced comparable pain relief over the entire treatment period, much better tolerability	[66,67]

b.i.d.: Twice daily; o.d.: Once daily; t.i.d.: Three-times daily.

0.5 Likert units on the Investigator Global Assessment of Disease Status) that remained relatively constant during the two extension periods.

Adverse events (AEs) possibly, probably or definitely drug-related were slightly more frequent for etoricoxib 90 mg (23%) and diclofenac 150 mg (24.5%) than for etoricoxib 30 mg (17.2%) or 60 mg (17.6%). More patients in the diclofenac group discontinued for AEs (11.8%) than in the etoricoxib groups (3.0–6.8%). GI nuisance symptoms were responsible for 4.0% of discontinuations with diclofenac and 0–2.1% with etoricoxib. Drug-related clinical AEs (upper respiratory infection, GI nuisance symptoms, diarrhea, influenza-like disease and others) occurred in 17.2–23.0% of the etoricoxib groups and in 24.5% of the diclofenac group. Lower extremity edema occurred in 6.7–8.4% of the etoricoxib groups versus 3.3% of the diclofenac group, CHF in two patients (2.7%) with etoricoxib 60 mg, and hypertension in 5.4–9.6% of etoricoxib groups versus 8.3% in the diclofenac group.

Etoricoxib 60 mg was found to be the minimal dose with the maximal efficacy, but in extension studies the 30-mg dose closely approximated that of etoricoxib 60 and 90 mg.

Reginster *et al.* evaluated the efficacy and safety of etoricoxib 60 mg once daily and naproxen 500 mg twice daily in a 138-week randomized, double-blind, parallel-group study of patients with OA of the knee or hip [61]. The study consisted of a 1-year study in two parts, Part I 12 weeks and Part II 40 weeks, followed by an 86-week extension. Patients who took placebo in Part I received etoricoxib or naproxen in Part II and the extension phase. Patients taking etoricoxib or naproxen in Part I remained on the same treatment throughout the entire length of the studies.

Of the 997 patients who entered the base studies, 615 completed them, and out of 463 patients who entered the extension phase, 161 and 151 in the etoricoxib and naproxen groups, respectively, completed 138 weeks of therapy.

Etoricoxib and naproxen showed similar efficacy throughout the 138 weeks of therapy. Clinically important treatment effects of etoricoxib and naproxen were observed from the first treatment period at week 2; these treatment effects were significantly superior to placebo during Part I. The WOMAC pain assessments for etoricoxib and naproxen were 67 and 67 mm (baseline), 28 and 29 mm (1 year), and 34 and 33 mm (138 weeks), respectively. Results for other efficacy end points were similar to those of the WOMAC pain assessments.

The percentage of patients with adverse experiences and serious adverse experiences was similar in all treatment groups. The naproxen group had the largest percentage of discontinuations due to adverse experiences and the largest percentage of drug-related AEs. The most common AEs in all study periods were upper respiratory infection and hypertension. Although these studies were not powered to evaluate the relative risk of GI or CV events, the safety data suggest that etoricoxib has a more favorable GI safety and tolerability profile compared with naproxen, whereas naproxen had a lower incidence of CV events.

Table 4. Clinical efficacy of etoricoxib in acute pain (dental pain and dysmenorrhea).

Primary end point	Treatments	Results	Ref.
Acute pain: post-operative dental pain			
Total pain relief over 6 h (TOPAR6)	Etoricoxib 120 mg, versus oxycodone/acetaminophen 10 mg/650 mg versus codeine/acetaminophen 60 mg/600 mg versus placebo	Etoricoxib has significantly greater overall analgesic efficacy versus oxycodone/acetaminophen and versus codeine/acetaminophen All treatments were superior to placebo groups	[94]
	Etoricoxib 120 mg, versus oxycodone/ acetaminophen 10 mg/650 versus placebo	Total pain relief with etoricoxib was significantly superior than oxycodone/ acetaminophen	[95]
Total pain relief over 8 h (TOPAR8)	Etoricoxib 60, 120, 180 or 240 mg, versus placebo and ibuprofen 400 mg	Etoricoxib 120 mg once daily was the minimal dose providing maximal analgesic effect. Etoricoxib 120, 180 and 240 mg had a rapid onset of analgesic effect (24 min) that persisted more than 24 h. 8 h after dosing etoricoxib 120 mg, had superior analgesic effect versus placebo, ibuprofen and etoricoxib 60 mg.	[96]
	Etoricoxib 120 mg versus placebo, naproxen sodium 550 mg, or acetaminophen/codeine 600/60 mg	Etoricoxib 120 mg had a rapid onset of analgesic effect similar to naproxen and acetaminophen/codeine. Maximal pain relief persisted up to 8 h after dosing with etoricoxib and naproxen.	[97]
Acute pain: primary dysmenorrhea			
TOPAR8	Etoricoxib 120 mg versus naproxen sodium 550 mg versus placebo over the course of three consecutive cycles	The TOPAR8 score for etoricoxib and naproxen were significantly greater than that of placebo.	[98]

Recently, Puopolo undertook a 12-week, randomized, double-blind, placebo- and active-comparator- (etoricoxib 30 mg vs ibuprofen 2400 mg) controlled trial over 548 patients with OA of the hip or knee [62]. Drug efficacy was assessed using three co-primary end points: WOMAC Pain Subscale; WOMAC Physical Function Subscale; and Patient Global Assessment of Disease Status (PGADS). The results have shown that treatment with etoricoxib 30 mg once daily provides superior efficacy versus placebo and comparable clinical efficacy versus ibuprofen 2400 mg (800 mg three-times daily) for the treatment of OA of the hip and knee.

In another study, Bingham *et al.* compared the efficacy of etoricoxib 30 mg with celecoxib 200 mg in the treatment of OA in two multicenter, 26-week studies [63]. Both were double-blind, placebo-controlled, noninferiority studies, with 599 patients in study 1 and 608 patients in study two. The patients were randomized 4:4:1:1 to etoricoxib 30 mg once daily, celecoxib 200 mg once daily or one of two placebo groups for 12 weeks. After 12 weeks, placebo patients were evenly distributed to etoricoxib or celecoxib. Efficacy was assessed using WOMAC index, Pain Subscale, Physical Function Subscale and PGADS. Etoricoxib 30 mg once daily was at least as effective as celecoxib 200 mg once daily with similar safety and both were superior to placebo in the treatment of knee and hip OA.

Rheumatoid arthritis

Two multinational studies have established the efficacy of etoricoxib in the treatment of RA: Collantes *et al.* undertook an international 12-week study in 891 chronic NSAID users randomized to received placebo (n = 357), etoricoxib 90 mg once daily (n = 353) or naproxen 500 mg twice daily (n = 181; ratio 2:2:1) [64]. The primary efficacy measures included counts of tender and swollen joints, and patient and investigator global assessments of disease activity. Other secondary measures included the Stanford Health Assessment Questionnaire, patient global assessment of pain, and the percentage of patients who achieved ACR20 responder criteria response. Compared with patients receiving placebo, patients receiving etoricoxib and naproxen showed significant

Table 5. Clinical efficacy of etoricoxib in chronic low-back pain and ankylosing spondylitis.

Primary end point	Treatments	Results	Ref.
Chronic low back-pain			
Assessment of low-back pain intensity scale (0 to 100 mm VAS) over 4 weeks of treatment	Etoricoxib 60 or 90 mg compared with placebo over 12 weeks	Etoricoxib 60 and 90 mg o.d. had significantly better clinical efficacy than placebo, which was observed as early as 1 week after initiating treatment, was maximal at 4 weeks and was stably maintained over 3 months.	[99,100]
Ankylosing spondylitis			
Patient's assessment of spinal pain, patient's global assessment of disease activity, and the Bath Ankylosing Spondylitis Functional Index	Etoricoxib 90 or 120 mg o.d. versus naproxen 500 mg b.i.d. versus placebo over 6 weeks (Part I) and then versus naproxen 500 mg b.i.d. for another 46 weeks (Part II)	For all primary end points, in Part I, both doses of etoricoxib were statistically superior to placebo and to naproxen. In Part II at the end of 52 weeks, both doses of etoricoxib were statistically superior versus naproxen.	[101]
	Etoricoxib 90 mg or 120 mg o.d. versus naproxen 500 mg b.i.d. versus placebo over 6 weeks (Part I) and then versus naproxen 500 mg b.i.d. for another 46 weeks	Etoricoxib and naproxen were significantly superior to placebo	[102]

b.i.d.: Twice daily; o.d.: Once daily; VAS: Visual analog scale.

improvements in all efficacy end points ($p < 0.05$). Treatment responses were similar between the etoricoxib and naproxen groups for all end points. The percentage of patients who achieved ACR20 responder criteria response was 41% in the placebo group, 59% in the etoricoxib group and 58% in the naproxen group. Tolerability was assessed by AEs and routine laboratory evaluations and both etoricoxib and naproxen were generally well tolerated.

Matsumoto *et al.* evaluated the efficacy and tolerability of etoricoxib for the treatment of RA. Patients received placebo, etoricoxib 90 mg once daily or naproxen 500 mg twice daily [65]. A total of 816 patients (placebo = 323, etoricoxib = 323, naproxen = 170) were randomized and 448 completed 12 weeks of treatment (placebo = 122, etoricoxib = 230, naproxen = 96). The most common reason for discontinuation was lack of efficacy and significantly more patients discontinued due to lack of efficacy in the placebo and naproxen groups than in the etoricoxib group (54.5, 36.5, 21.7%, respectively; $p < 0.01$).

The primary efficacy measures were patient and investigator global assessments of disease activity and direct assessment of arthritis by counts of tender and swollen joints. On all four primary end points, etoricoxib was statistically superior to placebo ($p < 0.01$) and naproxen ($p < 0.05$). Naproxen was significantly better than placebo ($p < 0.01$). Treatment effects of etoricoxib were consistent independent of corticosteroid use for all primary end points,

Active treatments were not significantly different ($p > 0.05$) from placebo in the percentage of patients with any drug-related clinical AE. Only one serious AE was considered drug-related: atrial fibrillation in the naproxen group. The most frequent drug-related AE was GI. Consequently etoricoxib 90 mg produced better results than either placebo or naproxen with a good safety profile.

Gout

Two similar randomized, double-blind trials compared etoricoxib 120 mg once daily versus indomethacin 50 mg three-times daily for 8 days [66,67]. Both studies included over 100 patients (n = 150 and n = 189) aged 18 years or more presenting with clinically diagnosed gout within 48 h of onset. The primary end points were patient assessment of pain in the study joint over days 2–5 and the secondary end points were investigator and patient global assessment of response to treatment and tenderness of the study joint.

Etoricoxib showed efficacy comparable to indomethacin reduction of inflammation and pain relief in both studies. Drug-related AEs occurred significantly less frequently with etoricoxib (22.7 and 16.5%) than with indomethacin (46.7 and 37.2%; $p < 0.05$) although the overall experience rates were similar between treatment groups.

Safety & tolerability

GI tolerability & safety

Etoricoxib was generally well tolerated in all the randomized clinical trials of the drug to evaluate clinical efficacy. However, the randomized, double-blind, multi-center Etoricoxib versus Diclofenac Sodium Gastrointestinal Tolerability and Effectiveness (EDGE) trial was undertaken to assess the GI tolerability of etoricoxib, an important primary end point for all COX-2 inhibitors [68]. EDGE is a component of the larger Multinational Etoricoxib and Diclofenac Arthritis Long-term Program (MEDAL), which consists of three studies: EDGE (NCT00092703); EDGE II (NCT00092742); and MEDAL (NCT00250445) [69–71]. A total of 7111 patients with OA of knee, hip, hand or spine were randomized to receive etoricoxib 90 mg once daily (n = 3593), 1.5-times the maximum recommended dose for OA, or diclofenac sodium 50 mg three-times daily (n = 3518) for 1 year. Patients were treated for up to 16.5 months (mean duration: 9 months) and were allowed to take gastroprotective agents (such as proton pump inhibitors [PPIs]) and low-dose aspirin. The primary end point of the study was GI tolerability, defined as the cumulative incidence of patients discontinuing for any clinical or laboratory GI AE between treatment groups. The results showed the cumulative discontinuation rates per 100 patient years (PY) were 9.41 (95% CI: 8.33, 10.49) with etoricoxib and 19.23 (95% CI: 17.71, 20.74) with diclofenac, with a hazard ratio (HR) of 0.5 (95% CI: 0.43, 0.58; $p < 0.001$). Separately, discontinuation rates due to GI AE of a clinical or laboratory demonstrated that for clinical GI AE, the discontinuation rates per 100 PY were 9.12 (95% CI: 8.05, 10.19) with etoricoxib and 12.28 (95% CI: 11.02, 13.55) with diclofenac, HR 0.75 (95% CI: 0.64, 0.89; $p < 0.001$). For laboratory GI AE, the discontinuation rates per 100 PY were 0.29 (95% CI: 0.09, 0.48) with etoricoxib and 6.88 (95% CI: 5.91, 7.85) with diclofenac, HR 0.04 (95% CI: 0.02, 0.09; $p < 0.001$).

Etoricoxib treatment resulted in a relative risk (95% CI) of 0.50 ($p < 0,001$), or significantly reduced by 50% the rates of discontinuation for combined clinical and laboratory GI AEs between etoricoxib and diclofenac.

GI safety and tolerability data from the MEDAL program [71], which includes over 34,701 patients in standard clinical practice followed for a mean duration of 18 months (maximum: 40 months), have shown an absolute difference incidence in upper GI clinical events of 0.67 (95% CI: 0.57–0.77) per 100 PY with etoricoxib and 0.97 (95% CI: 0.85–1.10) per 100 PY with diclofenac, yielding a HR of 0.69 (0.57–0.83). However, rates of complicated upper GI clinical events were not different between groups.

GI perforations, ulcers and bleeding (PUB) events were evaluated as an exploratory end point and the major difference between study groups was in uncomplicated ulcers (etoricoxib: 0.35 per 100 PY, 95% CI: 0.28–0.43; diclofenac 0.63 per 100 PY; 95% CI: 0.54–0.74). The risk of uncomplicated upper GI events was reduced with etoricoxib versus diclofenac in patients taking aspirin for at least 75% of the study period (HR: 0.67; 95% CI: 0.47–0.96) as well as in those using aspirin less often or not at all (HR: 0.50; 95% CI: 0.35–0.71).

The incidence of upper GI clinical events was lower in the MEDAL program than in other outcome studies. In nearly 15,599 patients not using PPIs or low-dose aspirin regularly, there was no evidence of a decrease in complicated events; however, there was a 51% reduction in the relative risk of uncomplicated events. Uncomplicated events accounted for most of the difference seen in the effect of etoricoxib and diclofenac on upper GI events.

Uncomplicated events are important because of the need for medical follow-up, including potential testing, possible discontinuation of NSAIDs or the addition of PPIs or misoprostol.

Dyspepsia is the most common side effect with NSAIDs and the most common motive for discontinuation. Significantly less dyspepsia was observed with etoricoxib than with diclofenac, regardless of low-dose aspirin and PPI use.

Conversely, the rates of lower GI clinical events were 0.32 (0.25–0.39) per 100 PY with etoricoxib and 0.38 (0.31–0.46) per 100 PY with diclofenac, yielding an HR of 0.84 (0.63–1.13). Differences in GI discontinuation rates due to laboratory (hepatic) AEs between groups remained significant, the rates of incidence were 0.3 versus 5.0; 0.3 versus 1.5; and 0.3 versus 1.8 in the EDGE I, EDGE II and MEDAL studies, respectively.

The results of the MEDAL program confirm the finding of Ramey *et al.* in a combined analysis of all randomized, double-blind, clinical trials of chronic treatment with etoricoxib versus NSAIDs to compare the incidence of PUB [72]. Of the 5441 patients with OA, RA or AS pooled from all ten multinational trials (etoricoxib 60, 90 or 120 mg [n = 3226] versus NSAID [ibuprofen, diclofenac, ornaproxen, n = 2215]), the incidence of PUBs over 44.3 months was significantly lower with etoricoxib versus NSAIDs (cumulative incidence 1.24 vs 2.48%, $p < 0.001$; rate/100 PY 1.00 vs 2.47; relative risk [RR]: 0.48; 95% CI: 0.32–0.73).

We can conclude that etoricoxib has a substantially better GI tolerability and safety profile than nonselective NSAIDs. Etoricoxib use is also associated with a consistently lower incidence of upper GI clinical events, lower incidence of endoscopic ulcers, lower new use of gastroprotective agents and significantly fewer discontinuations due to digestive adverse experiences. These findings support development of etoricoxib as an alternative therapy with superior GI safety compared with nonselective NSAIDs [68].

Renovascular safety profile

Renovascular effects are known dose-related effects of COX inhibition and have been observed with all nonselective NSAIDs [73,74] and COX-2 inhibitors [75–78]. These effects include, specifically, edema, CHF, hypertension or attenuation of the effects of antihypertensive agents, and less frequently, acute renal failure.

The data from the MEDAL program showed a higher rate of CHF with etoricoxib 90 mg than with diclofenac, but the difference was not significant (CI: 0.7 vs 0.3) and no difference was seen with 60 mg [70]. Discontinuation edema were significantly more frequent with etoricoxib 90 mg than with diclofenac (CI: 1.1 vs 0.4), but rates were similar for 60 mg (CI: 0.8 vs 0.7). Discontinuation due to hypertension was statistically more frequent with both doses of etoricoxib than diclofenac (CI: 2.2 vs 1.6 in MEDAL 60 mg; 2.5 vs 1.1 in MEDAL 90 mg; 2.3 vs 0.7 in EDGE-I 90 mg; 2.5 vs 1.5 in EDGE-II 90 mg).

A recent meta-analysis by Zhang *et al.* evaluated the adverse effects of COX-2 inhibitors from randomized trials [79]. In the combined analysis of 116,094 participants from 114 trials, including 127 trial populations (40 rofecoxib, 37 celecoxib, 29 valdecoxib + parecoxib, 15 etoricoxib and 6 lumiracoxib), there were a total of 6394 composite renal events (2670 peripheral edema, 3489 hypertension, 235 renal dysfunction) and 286 arrhythmia events. Results indicated significant heterogeneity of renal effects across agents indicating no class effect. Compared with controls, rofecoxib was associated with increased risk of edema (RR: 1.43; 95% CI: 1.23–1.66), hypertension (RR: 1.55; 95% CI: 1.29–1.85), and renal dysfunction (RR: 2.31; 95% CI: 1.05–5.07) and increased with higher doses and treatment duration. Other agents like etoricoxib were not significantly associated with risk. However, in Europe the use of etoricoxib in patients with uncontrolled hypertension is contraindicated [202].

In conclusion, the incidence of edema- and CHF-related AEs with etoricoxib is low overall and generally similar to that of comparator NSAIDs. Etoricoxib, at the doses currently prescribed for chronic use (60 and 90 mg) as well as for acute pain and acute gouty arthritis (120 mg), has effects on blood pressure that are generally similar to NSAIDs. There is evidence of a shallow dose-related trend for etoricoxib in the incidence of hypertension-related AEs.

CV effects of COX-2 inhibition

PGI2, the main product of COX in endothelium, causes vasodilatation, inhibits platelet aggregation and smooth muscle cell proliferation *in vitro* [80]. Evidences suggests that COX-2 is the main COX isoform that contributes to PGI2 biosynthesis *in vivo* even in healthy subjects [2,80]. PGI2 modulates the CV effects of TXA2 *in vivo*, a potent agonist of platelet aggregation and vasoconstrictor involved in occlusive vascular syndromes. Several experimental evidences show that PGI2 also buffers the effects of TX on blood pressure, atherogenesis, hemostasis and cardiac damage [81]. It acts as a general constraint on any agonist that acts harmfully on these systems. Unlike aspirin and nonselective NSAIDs that inhibit both PGI2 and TX, coxibs reduce PGI2 biosynthesis *in vivo* while leaving unaltered TX formation [2,82].

The results of three randomized, placebo-controlled trials provide evidence about the CV risks of rofecoxib, celecoxib and valdecoxib [83–85]. The Adenomatous Polyp Prevention on Vioxx (APPROVe) trial, a study of patients with a history of colorectal adenomas, was stopped early because rofecoxib doubled the risk of major CV events (RR: 1.92; 95% CI: 1.19–3.11). These findings confirmed the increased risk of myocardial infarction previously seen in the Vioxx GI Outcomes Research (VIGOR) trial [86] and some observational studies [87]. The public announcement of the APPROVe results, which resulted in the withdrawal of rofecoxib from the market in September 2004, prompted scientists to review the CV-safety results of a similar trial, the Adenoma Prevention with Celecoxib (APC) study [84]. In the APC trial celecoxib 200 or

400 mg twice daily was associated with a risk of CV events three-times higher (RR: 2.8; 95% CI: 1.3–6.3).

The third COX-2 inhibitor trial evaluated the CV toxicity of another coxib, valdecoxib (and its intravenous prodrug, parecoxib). The short-term use of valdecoxib and parecoxib was associated with increased CV risk in patients undergoing coronary artery bypass surgery treated with aspirin [85].The EMEA has concluded that the available data show an increased risk of CV AEs associated with use of COX-2 inhibitors as a class [202]. In fact, the mechanism associated with the CV toxicity of these drugs relates to the inhibition of PGI2, disabling one of the primary defenses of the endothelium against platelet aggregation, hypertension and atherosclerosis [81]. COX-2 inhibitors also promote an imbalance in favour of vasoconstriction.

Although etoricoxib has been evaluated in a number of clinical trials, the MEDAL program was designed to compare the effects of etoricoxib and diclofenac on CV and GI outcomes in standard clinical practice [69–71]. MEDAL was a prespecified, noninferiority comparison of CV risk; the primary analysis was a prespecified, pooled, per-protocol analysis of three double-blind randomized comparisons of etoricoxib (60 or 90 mg once daily) and diclofenac (150 mg daily) in 34,701 patients with OA or RA followed for a mean duration of 18 months (maximum: 40 months). To be eligible for enrollment, patients had to be aged 50 years or older with a clinical diagnosis of OA of the knee, hip, hand or spine, or a clinical diagnosis of RA meeting at least four of seven of the American Rheumatism Association 1987 revised criteria and, in the judgment of the investigator, would need chronic treatment with an NSAID.

Table 6 shows the baseline characteristics of the MEDAL patient population. The patients enrolled exhibited a range of CV risks. Approximately 38% had increased CV risk at baseline (defined as at least two CV risk factors and/or a history of symptomatic atherosclerotic CV disease). Approximately 35% were low-dose aspirin users. Patients with a history of myocardial infarction, coronary artery bypass graft or percutaneous coronary intervention more than 6 months preceding the study were enrolled.

The composite primary end point was arterial and venous thrombotic CV events (first occurrence of fatal and nonfatal events: myocardial infarction [including silent infarction], unstable angina pectoris, intracardiac thrombus, resuscitated cardiac arrest, thrombotic stroke, cerebrovascular thrombosis, transient ischemic attack, peripheral venous thrombosis, pulmonary embolism, peripheral arterial thrombosis and sudden or unexplained death). Predefined safety end points also included discontinuations due to hypertension, edema, renal dysfunction, GI AEs (bleeding, perforation, obstruction or ulcer), and liver test abnormalities or other hepatic events. In order to simulate the criteria of daily practice, patients with CV risk factors were allowed to take low-dose aspirin and patients with GI risk factors were allowed to take antiulcer medication (PPIs or misoprostol).

Table 7 presents the incidence of CV events. The HR for the per-protocol comparison of any thrombotic events in the two groups was 0.95 (95% CI: 0.81–1.11), which demonstrated the noninferiority of etoricoxib to diclofenac. The HR for etoricoxib versus diclofenac for cardiac events, cerebrovascular events and peripheral vascular events did not show any discernible difference between treatment groups, the most common thrombotic CV event in both groups being nonfatal or fatal myocardial infarction (etoricoxib: 0.43 per 100 PY; diclofenac: 0.49 per 100 PY). Rates of fatal thrombotic CV events were similar (both 0.17 per 100 PY).

In addition, there were no significant differences in thrombotic CV events by subgroups, suggesting that the thrombotic CV risk of etoricoxib did not differ across the subgroups analyzed, despite varying baseline CV risk and etoricoxib dose.

Fatal thrombotic CV events had the same rate of occurrence with both drugs (0.17 per 100 PY). All-cause mortality rates were 0.48 per 100 PY for etoricoxib and 0.50 per 100 PY for diclofenac in the ITT population through 14 days after study drug discontinuation. Thrombotic CV events did not vary in subgroup analysis, suggesting that the thrombotic CV risk of etoricoxib versus diclofenac did not differ across the subgroups analyzed, including varying baseline CV risk and etoricoxib dose. CV event rates varied with CV risk ranging from less than one event per 100 PY in patients with no established atherosclerotic CV disease and one or no CV risk factors, to more than three events per 100 PY in patients with established atherosclerotic CV disease. The 90-mg dose of etoricoxib was associated with a higher rate of CHF and edema than diclofenac, although the difference was not significant; no difference was seen with etoricoxib 60 mg.

Table 6. Baseline characteristics of the MEDAL patient population.		
	Etoricoxib (n = 17,412)	**Diclofenac (n = 17,289)**
Age, mean (SD)	63.2 (8.5)	63.2 (8.5)
Women	12,925 (74.2%)	12,823 (74.2%)
Arthritis type*		
–Osteoarthritis	12,533 (72.0%)	12,380 (71.6%)
–Rheumatoid arthritis	4878 (28.0%)	4909 (28.4%)
Weight in kg, mean (SD)	78.9 (18.6)	78.9 (18.5)
BMI in kg/m^2, mean (SD)	29.5 (18.6)	29.5 (6.0)
Diabetes	1810 (10.4%)	1855 (10.7%)
Hypertension‡	8109 (46.6%)	8221 (47.6%)
Dyslipidemia‡	5097 (29.3%)	5034 (29.1%)
Current cigarette smoker	2034 (11.7%)	2037 (11.8%)
Established atherosclerotic CV disease§	2014 (11.6%)	2010 (11.6%)
Two or more CV risk factors¶ or established atherosclerotic CV disease	6586 (37.8%)	6639 (38.4%)
History of upper GI event	1127 (6%)	1133 (7%)
Low-dose aspirin use	6030 (34.6%)	5976 (34.6%)
PPI use	6741 (39%)	6664 (39%)
Cardiac medications		
–β-blocker	2806 (16.1%)	2837 (16.4%)
–ACE inhibitor or ARB	4571 (26.3%)	4535 (26.2%)
–Calcium channel blocker	2096 (12.0%)	2149 (12.4%)
–Statin	2859 (16.4%)	2890 (16.7%)
–Diuretic	3129 (18.0%)	3147 (18.2%)
Anti-arthritic medications		
–COX-2 selective NSAID	4873 (28.0%)	4939 (28.6%)
–Traditional NSAID	14 209 (81.6%)	14 174 (82.0%)
–Acetaminophen	10 852 (62.3%)	10 765 (62.3%)
–High-dose aspirin	173 (1.0%)	185 (1.1%)
–Glucocorticoid	2758 (15.8%)	2762 (16.0%)
–Methotrexate	2762 (16%)	2831 (16%)
–Other DMARDs#	2246 (12.9%)	2208 (12.8%)

Data are number (%) unless otherwise specified.
ACE: Angiotensin-converting enzyme; ARB: Angiotensin-receptor blocker; BMI: Body mass index; CV: Cardiovascular; MEDAL: Multinational Etoricoxib and Diclofenac Arthritis Long-term; PPI: Protein-pump inhibitor.
**Data missing for one patient.*
‡At time of screening.§Includes clinical history of myocardial infarction, angina pectoris, cerebral vascular accident, transient ischemia attack, angioplasty, carotid artery disease, peripheral vascular disease, or coronary artery bypass surgery.
¶Includes two or more of the following risk factors: history of hypertension, diabetes, dyslipidemia, family history of CV disease, current cigarette smoking.
#Disease-modifying antirheumatic drug.
Data taken from [70].

Discontinuations due to edema were significantly more frequent with the 90 mg dose of etoricoxib than with diclofenac; however, discontinuation rates were similar for the 60 mg dose of etoricoxib and diclofenac. Discontinuations due to hypertension were more frequent with both doses of etoricoxib than with diclofenac.

In each individual study, anti-arthritic efficacy was expressed as the average change from baseline in patient global assessment of disease status (on a scale of 0 to 4) using an analysis of covariance model. Etoricoxib and diclofenac showed similar efficacy for the treatment of arthritis, with average changes from baseline in

Table 7. Incidence of cardiovascular and gastrointestinal events in the population of the MEDAL Program.

	Etoricoxib (n = 16,819; 25,836 PY)*		Diclofenac (n = 16,483; 24,766 PY)		HR (95% CI)
	Patients n (%)‡	Rate§	Patients n (%)‡	Rate§	
Cardiovascular events in per protocol population¶					
Fatal thrombotic CV events	43 (0.26)	0.17 (0.12–0.22)	43 (0.26)	0.17 (0.13–0.23)	0.96 (0.63–1.46)
Cardiac events (non-fatal/fatal myocardial infarction, sudden cardiac death, unstable angina pectoris, resuscitated cardiac arrest, cardiac thrombus)	183 (0.62)	0.71 (0.61–0.82)	194 (1.18)	0.78 (0.68–0.90)	0.90 (0.74–1.10)
Cardiovascular events (non-fatal/fatal ischemic cerebrovascular stroke, cerebrovascular venous thrombosis, transient ischemic attack)	89 (0.53)	0.34 (0.28–0.42)	79 (0.48)	0.32 (0.25–0.40)	1.08 (0.80–1.46)
Peripheral vascular events (non-fatal/fatal pulmonary embolism, non-fatal/fatal peripheral arterial thrombosis, peripheral venous thrombosis)	53 (0.32)	0.20 (0.15–0.27)	55 (0.33)	0.22 (0.17–0.29)	0.92 (0.63–1.35)
Upper gastrointestinal clinical events in intent-to-treat population#					
Any clinical GI event	176 (1.01%)	0.67	246 (1.42%)	0.97	0.69 (0.57–0.83)
Complicated GI events (perforation, obstruction, bleeding of gastric, duodenal, gastric/duodenal or anastomotic ulcer, other bleeding)	78 (0.45%)	0.30	82 (0.47%)	0.32	0.91 (0.67–1.24)
Uncomplicated GI events (bleeding of gastric, duodenal or gastric/duodenal ulcer)	98 (0.56%)	0.37	164 (0.95%)	0.65	0.57 (0.45–0.74)

Patients with several events were listed for each of their specific diagnoses.
GI: Gastrointestinal; MEDAL: Multinational Etoricoxib and Diclofenac Arthritis Long-term; PY: Patient-years.
**Etoricoxib combined, 60 mg and 90 mg.*
‡Crude incidence (n/Nx100).
§Events per 100 patient-years.
¶Per-protocol analysis includes only those events that occur in patients while on the study treatment of within 14 days thereafter; patients who took study medication less than 75% or non-study NSAIDs more than 10% of the time while on study medication were excluded from the analysis (approximately 4% of total MEDAL Program population.#Intent-to-treat analysis includes patients followed to the end of their respective study, no matter when they stopped their study medication and no matter what other medications they took after stopping their study medication.
Data taken from [70].

patient-reported global assessment of disease status of -0.67 (SD: 1.02) for etoricoxib and -0.61 (SD: 1.02) for diclofenac (Likert units). Discontinuations due to lack of efficacy were similar between groups.

Many authors have criticized the selection of diclofenac as the comparator in MEDAL [88,89]. Diclofenac was used as the comparator because it is the most widely prescribed NSAID in the world, has been approved by the FDA since 1988, and is used by as many as 20 million people. In fact, alarm about the possible CV thrombotic effects of diclofenac arose after the withdrawal of rofecoxib from the market in 2004, rather than from the prolonged earlier experience with diclofenac. At the Joint Meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee (FDA) in February 2005, during a discussion of standards for approval of new NSAIDs, the Committee recommended that future studies include primarily naproxen as a comparator, although ibuprofen could be studied as a typical NSAID and diclofenac as a model of a relatively selective traditional NSAID. Comparisons with either naproxen or an NSAID combined with a PPI were considered appropriate for evaluating GI risk. The upper confidence boundary against naproxen was required to be neutral or better than neutral [203].

However, the MEDAL study has been characterized as comparing two COX-2-selective agents because diclofenac has some COX-2 selectivity. However, many other so-called 'non-selective' NSAIDs show some degree of COX-2 selectivity (e.g., nimesulide and meloxicam show a level of COX-2 selectivity similar to that of diclofenac, whereas indomethacin and naproxen are preferential COX-1 inhibitors [3]). Moreover, in accordance with COX-1/COX-2 IC_{50} results, diclofenac (COX-1/COX-2 IC_{50}: 29) is more than ten-times less COX-2-selective than etoricoxib (COX-1/COX-2 IC_{50}: 344).

The authors of the MEDAL program support the choice of diclofenac as an appropriate comparator agent. Unlike naproxen or ibuprofen, diclofenac does not interfere with the antiplatelet effects of low-dose aspirin, which was used by approximately 35% of the MEDAL participants and, consequently, a large number of the participants with confirmed CV risk factors or atherosclerotic disease who were, perhaps, the most important subgroup of patients, given the primary end point of CV thrombotic events of MEDAL. Additionally, diclofenac, like other traditional NSAIDs (ibuprofen), significantly increases the incidence of gastroduodenal ulcers compared with placebo and higher than those with selective COX-2 inhibitors [90].

Nevertheless, in April 2007, the FDA's Arthritis Drugs Advisory Committee has delivered a resounding 'no' vote to etoricoxib. A total of 20 arthritis committee members voted against approval and only one member of the FDA's Gastrointestinal Drugs Advisory Committee, recommended it. Panelists expressed concern over the use of diclofenac as the comparator drug in MEDAL, arguing that the better comparator would have been naproxen plus a PPI, and, the benefits on the control of pain, similar to other NSAIDs, and the improved GI safety, are not justified by the potential CV risk, with the possibility of edema, hypertension, CHF or MI.

In 2006 Kearney *et al.* presented a meta-analysis of published and unpublished tabular data from randomized trials, with indirect estimation of the effects of traditional NSAIDs and COX-2 on serious vascular events [31]. Overall, the incidence of serious vascular events was similar between a selective COX 2 inhibitor and any traditional NSAID (1.0%/year vs 0.9%/year; 1.16, 0.97–1.38; p = 0.1). However, statistical heterogeneity (p = 0.001) was found between trials of a selective COX-2 inhibitor versus naproxen (1.57, 1.21–2.03) and of a selective COX-2 inhibitor versus non-naproxen NSAIDs (0.88, 0.69–1.12). The summary rate ratio for vascular events, compared with placebo, was 0.92 (0.67–1.26) for naproxen, 1.51 (0.96–2.37) for ibuprofen and 1.63 (1.12–2.37) for diclofenac. They concluded that selective COX-2 inhibitors are associated with a moderate increase in the risk of vascular events, as are high-dose regimens of ibuprofen and diclofenac, but high-dose naproxen is not associated with such an excess.

However, also in 2006, Anderson *et al.* examined the risk of ischemic stroke associated with COX-2 inhibitors in a nested case–control study in a cohort of 469,674 patients registered within the UK General Practice Research Database, who had at least one prescription of an NSAID [91]. A total of 3094 cases with ischemic stroke were identified and 11,859 controls were matched on age, sex, year. The odds ratio (OR) of coxibs were: for current use of rofecoxib (OR: 1.71; 95% CI: 1.33–2.18), for etoricoxib (OR: 2.38; 95% CI: 1.10–5.13), and for celecoxib (OR: 1.07; 95% CI: 0.79–1.44). ORs tended to increase with higher daily dose and longer duration of use and were also elevated in patients without major stroke risk factors. This data suggests that COX-2 selective NSAIDs differ in their potential to cause ischemic cerebrovascular events. An increased risk of ischemic stroke may be influenced by additional pharmacological properties of individual COX-2 inhibitors.

Based on these studies, the US FDA requested that the labeling for all NSAIDs, including COX-2 selective inhibitors as well as traditional NSAIDs, include warnings related to the appearance of atherothrombotic events [204]. In Europe, the EMEA established individual commissions of evaluation of the NSAIDs after these events and concluded that there is a small increase of associated risk of MI with the use of traditional NSAIDs, mainly with high doses and prolonged use. In spite of this, the benefit–risk balance of these drugs continues to be favorable [202].

Regulatory affairs

Etoricoxib is a highly selective COX-2 inhibitor that has been approved in Europe as a once-daily medicine for symptomatic relief in the treatment of OA, RA, acute gouty arthritis and AS [38]. It was recently approved in Mexico, Brazil and Peru for other indications, such as relief of acute pain associated with dental surgery and primary dysmenorrhea and chronic musculoskeletal pain, including chronic low-back pain. Nonetheless, the FDA has declared that additional safety and efficacy data are required before the New Drug Application for etoricoxib can be approved in USA.

Conclusion

In a number of clinical trials, etoricoxib has been shown to be a selective COX-2 inhibitor. Its GI safety profile has been found to be markedly better than that of other NSAIDs, such as diclofenac, naproxen and ibuprofen. Its CV profile is acceptable for patients with a low CV risk. The anti-inflammatory and analgesic efficacy of etoricoxib is comparable to that of nonselective NSAIDs in diverse disease settings, particularly OA, and may be superior in RA and in the relief of gout pain. In South America, it has also been authorized for primary dysmenorrhea, post-operative dental pain, chronic low-back pain, and AS. etoricoxib has been shown to reach its peak effect in approximately 6 weeks and to conserve this effect throughout treatment in trials up to 40 months with good tolerance.

Etoricoxib is particularly suitable for patients with an indication for use and risk of GI adverse effects with no risk or a low risk of CV events. Likewise, it is not advisable in patients with severe kidney or liver disease, as is the case with other NSAIDs. In patients who satisfy these conditions, etoricoxib is an effective and safe drug.

Future perspective

After the APPROVe trial showed a twofold increase in CV risk compared with placebo, rofecoxib was voluntarily removed from the worldwide marketplace in 2004. In 2005, valdecoxib was also removed after problems emerged with use in high-risk patients after coronary artery bypass graft. This year the FDA advisory committees formally recognized the CV and cerebrovascular risk of coxibs as a class. They recommended banning direct-to-consumer advertising of COX-2 inhibitors and individually tailored 'black box' warnings for the CV risk [26]. At the same time, in June 2005, the Committee on Human Medicinal Products of the EMEA recommended a number of restrictions on the use of all drugs of this type (celecoxib, etoricoxib, valdecoxib and parecoxib) and took the precautionary measure of prohibiting the use of COX-2 inhibitors in patients with established ischemic heart disease and/or cerebrovascular disease, as well as in patients with peripheral arterial disease [92]. Likewise, they advised health care professionals to exercise caution in prescribing COX-2 inhibitors to patients with risk factors for heart disease, such as hypertension, hyperlipidemia, diabetes and smoking, and to use the lowest effective dose for the shortest possible duration of treatment. Nonetheless, the EMEA concluded that COX-2 inhibitors had a positive benefit–risk balance in their target patient populations and that COX-2 inhibitors and some conventional NSAIDs required further review by the Committee's Pharmacovigilance Working Party.

In October 2006, in light of evidence from clinical trials, the EMEA issued a new opinion reiterating the recommendation to use the lowest effective dose for the shortest possible time to control symptoms and advising prescribers to choose any NSAID based on the overall safety profile and the patient's individual risk factors, as well as to avoid switching between NSAIDs without carefully considering these factors and the patient's individual preferences. The scientific evidence cited relevant to etoricoxib indicated that for the majority of patients, the potential increase in thrombotic risk is small, but in subjects with pre-existing CV risk factors or a history of CV disease, the risk may be higher [93].

The evidence of MEDAL and other clinical trials indicates that the benefits of etoricoxib outweigh its disadvantages. Given the subjective nature of pain relief and the variety of concomitant conditions present in patients requiring the use of anti-inflammatory medications, many physicians find the range of selective and nonselective NSAIDs available ideally suited to personalizing treatment for each patient depending on their risk profile. However, in April 2007, the FDA's Arthritis Drugs Advisory Committee declined to approve etoricoxib for be used in the USA because the benefits on the control of the pain is similar to other NSAIDs, and the high profile of security GI are not justified by the CV risk.

More studies who compare between COX-2 molecules and new safety dates about traditional NSAID are necessary to dilucidate CV risk. Etoricoxib is one of the options within a range of products that is particularly appropriate for gout, dental extractions, dysmenorrhea and other conditions requiring a rapid effect, as well as OA, RA and AS in patients at low CV risk but with an increased risk of GI complications including dyspepsia, a minor problem but one of the most common reasons for discontinuing NSAIDs.

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Executive summary

Background

- Nonsteroidal anti-inflammatory drugs (NSAIDs) are standard of care for the treatment of pain, fever and inflammatory diseases dependent of the inhibition of cyclooxigenase (COX)-2, with unwanted side-effects dependent of COX-1: gastrointestinal toxicity, inhibition of platelet aggregation and aspirin-sensitive asthma.
- Etoricoxib is one of the latest COX-2-selective inhibitors developed with a low gastrointestinal side effects.

Phamacolodynamics & pharmacokinetics of etoricoxib

- Etoricoxib is 100-fold more selective for COX-2 than COX-1.
- After single doses of etoricoxib maximal COX-2 inhibition occurs in 1.5 h.
- Repeated oral dosing allows a profound inhibition still to be present at 24 h.
- Etoricoxib is well absorbed with low clearance resulting in a half-life of 27 h.
- Etoricoxib has an extensively liver P450-dependent oxidation to 6´-hydroxymethyl and 6´-carboxylic acid derivative (the major metabolite). Both are inactive.
- The excretion of both metabolites are mainly urinary (70%), with only 20% of a dose appearing in feces.
- Less than 1% of etoricoxib is recovered intact in urine.

Clinical efficacy

- Phase IIb/III clinical trials have shown that etoricoxib (60 or 90 mg) provides clinically meaningful benefit to patients with osteoathritis (OA), with an efficacy similar to that of diclofenac (150 mg) or naproxen (1000 mg) over 1 year of treatment. Clinical trials and regulatory filings have shown 30 mg to be effective in OA. Given that there are recommendations for using the lowest possible dose for the shortest period of time from all regulatory and professional organizations, it should be recommended to follow guidelines and advocate for approval of this dose, which is effective in OA.
- For rheumatoid arthritis, etoricoxib (90 mg) was statistically superior to placebo and naproxen (1000 mg).
- In gouty patients, etoricoxib 120 mg showed efficacy comparable with indomethacin (150 mg) in reduction of inflammation and pain relief.
- In ankylosing spondylitis, etoricoxib 90 mg (and 120 mg) were statistically superior to placebo and to naproxen.

Safety & tolerability

- The Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program has compared the effects of etoricoxib and diclofenac on cardiovascular and gastrointestinal outcomes in standard clinical practice.
- Upper gastrointestinal clinical events were significantly less frequent with etoricoxib than with diclofenac. Discontinuation due to liver test abnormalities were also significantly less frequent with etoricoxib than diclofenac.
- No difference were seen in the thrombotic events, cardiac events, cerebrovascular events and peripheral vascular events between etoricoxib or diclofenac.
- Etoricoxib 90 mg (not 60 or 30 mg) was associated with a higher rate of congestive heart failure and edema.
- Hypertension was more frequent with both doses of etoricoxib than with diclofenac.

Dosage & administration

- Recommended dosages are:
  - Osteoarthritis: 30 or 60 mg once daily
  - Rheumatoid arthritis: 90 mg once daily
  - Gouty arthritis: 120 mg once daily

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Affiliations

- *Alejandro Escudero-Contreras, MD, Master of Methodology Research and Rheumatologist, Rheumatology Service*
  "Reina Sofia" University Hospital, Rheumatology Department, Córdoba, Spain
- *Janitzia Vazquez-Mellado Cervantes, MD, PhD, Professor of Methodology Research and Rheumatologist, General Hospital of México, Rheumatology Department, México DF, México*
- *Eduardo Collantes-Estevez, MD, Professor of Rheumatology at the University Of Córdoba. Spain and Chief Service*
  "Reina Sofia" Univerity Hospital, Department of Rheumatology, Avda. Menendez Pidal s/n, 14004 Córdoba, Spain
  Tel.: +34 957 011 631;
  Fax: +34 957 011 683;
  eduardo.collantes.sspa@juntadeandalucia.es