DRUGDEX® Evaluations

ETORICOXIB

0.0 Overview

1) Class

a) This drug is a member of the following class(es):
Cyclooxygenase-2 Inhibitor

2) Contraindications

a) Previous hypersensitivity to etoricoxib

b) Acute peptic ulcer disease or GI bleeding

c) Patients with a history of bronchospasm with rhinoconjunctivitis or urticaria/angioedema associated with aspirin or other nonsteroidal antiinflammatory agents (adult-onset asthma, chronic rhinitis, nasal polyps, and chronic urticaria/angioedema predispose to these reactions) (risk of anaphylactic-like reactions)

d) Severe renal or hepatic disease

1.0 Dosing Information

1.1 Drug Properties

A) Information on specific products and dosage forms can be obtained by referring to the Tradename List (Product Index)

B) Synonyms
Etoricoxib

2.0 Pharmacokinetics

Onset and Duration

Drug Concentration Levels

ADME

2.1 Onset and Duration

A) Onset

1) Initial Response

a) DENTAL PAIN, ORAL: 25 to 30 minutes [21][22].

1) Value indicates time to perceptible pain relief after an oral dose of 120 mg.

B) Duration

1) Single Dose

a) DENTAL PAIN, ORAL: at least 24 hours (120 to 240 mg, single dose) [21][22].

1) An analgesic duration of 12 hours has been reported after 60-mg single doses [21].

2.2 Drug Concentration Levels

A) Therapeutic Drug Concentration

1) Not established. Plasma-level monitoring is not used clinically.

B) Time to Peak Concentration

1) ORAL, TABLET: 1.5 hours (120 mg) [23][24].

a) With oral doses of 5 to 40 mg, peak levels occurred in approximately 1 hour [24].

b) Mean peak plasma concentrations of 201, 411, 788, and 2186 ng/mL were reported after single oral doses of 10, 20, 40, and 120 mg, respectively, in healthy subjects. Plasma levels fell to less than 400 ng/mL within 48 hours of all doses [24]. Results of this study suggested linearity of etoricoxib pharmacokinetics over the range of 5 to 120 mg.

C) Area Under the Curve

1) 33 to 41 mcg x hr/mL (mean values; 120 mg doses) [23][24].

a) With single oral doses of 10, 20, 40, and 120 mg in healthy subjects, mean AUC values were 1.5, 6.7, 13.3, and 40.6 mcg x hr/mL, respectively [24].

b) In a further study of healthy subjects receiving repeat dosing with 100 mg once daily for 9 days, the mean AUC was 12 mcg x hr/mL after the first dose and 19 mcg x hr/mL on day 9 [25]

c) In a multiple-dose study of 24 healthy patients for 10 days, the mean AUC after the 10th etoricoxib 120-milligram once-daily dose [26].

d) AUC was unaffected by a high-fat meal before a 120-milligram dose [26].

2.3 ADME

Absorption

Distribution

Metabolism

Excretion

Elimination Half-life

2.3.1 Absorption

A) Bioavailability

1) ORAL, TABLET: 80% to 100% [26][27].

a) In one study, the pharmacokinetics of etoricoxib appeared similar with use of four different tablet formulations [24].

b) Antacids (calcium carbonate, aluminum/magnesium hydroxide) do not significantly affect the absorption of etoricoxib [23].

B) Effects of Food

1) decreased rate of absorption but no effect on extent of absorption [26].

a) A 120-milligram dose administered after a high-fat meal resulted in 36% lower Cmax and a 2-hour delay in tmax, but no change in AUC [26].

2.3.2 Distribution

A) Distribution Kinetics

1) Volume of Distribution

a) 119 L at steady state following 24- milligram single intravenous dose [26].

2.3.3 Metabolism

A) Metabolism Sites and Kinetics

1) LIVER, at least 90% [27][28].

a) The major metabolic pathway is 6'-methyl hydroxylation, primarily via cytochrome P450 (CYP)-3A4. Other metabolites include the 1'-N-oxide, 6'-carboxylic acid, and 6'-hydroxylated glucuronide. To a lesser extent, CYP-2D6, CYP-2C9, CYP-1A2, and CYP-2C19 are also involved in metabolism. No metabolites are considered to contribute significantly to COX-2 (or COX-1) inhibition [27][28].

b) Etoricoxib is not a potent inducer or inhibitor of CYP-3A4; it is unlikely that the drug (or its metabolites) will interact with compounds metabolized by CYP-3A4 [28]. However, this requires confirmation.

2.3.4 Excretion

A) Kidney

1) Etoricoxib is excreted in the urine, primarily as metabolites [27]; quantitative data are unavailable.

B) Other

1) OTHER EXCRETION

a) TOTAL BODY CLEARANCE

1) 0.049 L/minute following 25-milligram single intravenous dose [26].

b) FECES, extent unknown [27].

1) Etoricoxib is excreted in the feces, primarily as metabolites [27]; quantitative data (including degree of biliary excretion) are unavailable.

2.3.5 Elimination Half-life

A) Parent Compound

1) ELIMINATION HALF-LIFE

a) 22 hours [24].

1) Value after single doses of 5 to 120 mg in healthy subjects; no apparent dose-dependency.

2) Value after single doses of 30 to 120 milligrams (mg) and multiple doses of 120 mg for 10 days in healthy subjects [26].

3.0 Cautions

Contraindications

Precautions

Adverse Reactions

Drug Interactions

3.1 Contraindications

A) Previous hypersensitivity to etoricoxib
B) Acute peptic ulcer disease or GI bleeding
C) Patients with a history of bronchospasm with rhinoconjunctivitis or urticaria/angioedema associated with aspirin or other nonsteroidal antiinflammatory agents (adult-onset asthma, chronic rhinitis, nasal polyps, and chronic urticaria/angioedema predispose to these reactions) (risk of anaphylactic-like reactions)
D) Severe renal or hepatic disease

3.2 Precautions

A) History of mild allergic phenomena related to ingestion of other nonsteroidal antiinflammatory drugs (eg, rash)
B) Conditions predisposing to gastrointestinal events (eg, history of peptic ulcer, upper gastrointestinal disease, ulcerative colitis; smoking; advancing age; concurrent aspirin or corticosteroids; alcohol abuse; stress)
C) Patients with hypertension, recent MI, angina, or other cardiovascular disease (potential for fluid retention; etoricoxib may possess prothrombotic activity)
D) Patients with bleeding disorders (potential exacerbation)
E) Mild or moderate liver disease (pharmacokinetic data lacking; enhanced risk of adverse events, such as fluid retention)
F) Mild or moderate renal impairment (pharmacokinetic data lacking; potential for adverse renal effects, particularly in the elderly); there is no convincing evidence that COX-2 selectivity reduces the risk of renal toxicity relative to nonselective agents
G) Patients with risk factors for renal failure (eg, diabetes, preexisting edema, hypovolemia, sepsis); there is no convincing evidence that COX-2 selectivity reduces the risk of renal toxicity relative to nonselective agents

3.3 Adverse Reactions

Cardiovascular Effects

Gastrointestinal Effects

Neurologic Effects

3.3.1 Cardiovascular Effects

Cardiovascular event risk

Cardiovascular finding

Thromboembolic disorder

3.3.1.A Cardiovascular event risk

See Drug Consult reference: CARDIOVASCULAR AND CEREBROVASCULAR RISK OF COX-2 SELECTIVE AND NON-SELECTIVE NSAIDS

3.3.1.B Cardiovascular finding

1) Small increases in blood pressure have been reported with doses of 60 or 90 mg daily in unpublished studies [9].
2) In one study involving healthy subjects, no significant effect on platelet aggregation, bleeding time, or serum thromboxane B2 was observed with etoricoxib in doses up 150 mg once daily for 9 days [10].
3) Unpublished study results suggest that once-daily doses of etoricoxib 120 mg do not interfere with antiplatelet effects of low-dose aspirin [11].

3.3.1.C Thromboembolic disorder

1) According to the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program (prospective pooled data from 3 randomized, double-blind clinical trials: MEDAL, EDGE and EDGE II) there was a comparable risk of a composite of thrombotic cardiovascular events in etoricoxib- and diclofenac- treated osteoarthritis and rheumatoid arthritis patients. Long term administration of study drugs for 18 months duration included etoricoxib 60 or 90 mg orally once daily (n=17,412) or diclofenac 150 mg orally daily (either 75 mg orally twice daily or 50 mg three times daily; n=17,289). The primary composite thrombotic endpoint consisted of the first occurrence of fatal and non-fatal events including myocardial infarction (MI), unstable angina, 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. In the etoricoxib group (n=16,819), the event rate for thrombotic events was 1.24 per 100 patient-years (n=320/25,836 patient-years at risk), and in the diclofenac group (n=16,483), the event rate was 1.3 per 100 patient-years (n=323/24,766 patient-years at risk) (hazard ratio (HR), 0.95; 95% confidence interval (CI), 0.81 to 1.11). The most common thrombotic cardiovascular event was non-fatal or fatal MI, with rates of 0.43 per 100 patient-years in the etoricoxib group compared with 0.49 per 100 patients years in the diclofenac group. The incidence of fatal thrombotic cardiovascular events was 0.17 per 100 patient-years in both groups (HR, 0.96; 95% CI, 0.63 to 1.46) [12].

2) An increased risk of thrombotic events has been observed during etoricoxib treatment of osteoarthritis (unpublished study results). The incidence of thrombotic complications was 3.2% in patients receiving etoricoxib compared to 0.8% in those treated with naproxen; events with etoricoxib included myocardial infarction, unstable angina, ischemic stroke, and transient ischemic attacks [11][9]. Rofecoxib was also associated with a increased risk of thrombotic events in one trial (Vioxx(R) VIGOR GI Safety Trial) [11]. Both drugs are manufactured by Merck; the manufacturer has designed large cardiovascular safety trials to clarify the prothrombotic risk potential with each agent [9]. Concurrent aspirin use will be permitted in these trials.

3.3.4 Gastrointestinal Effects

3.3.4.A Gastrointestinal tract finding

1) According to results from the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program, there were significantly fewer upper gastrointestinal (GI) events and uncomplicated GI events with etoricoxib than with diclofenac in patients with osteoarthritis and rheumatoid arthritis; however, there were no significant differences in complicated GI events between the groups. The MEDAL program (n=34,701) was prospectively designed to pool data from 3 randomized, double-blind clinical trials: MEDAL (n=23,504), etoricoxib vs diclofenac sodium GI tolerability and effectiveness study (EDGE; n=7111), and EDGE II (n=4086). The patients were randomly assigned etoricoxib 60 or 90 mg orally daily (n=17,412) or diclofenac 150 mg orally daily (n=17,289). The most common GI events were uncomplicated ulcer and complicated or uncomplicated upper GI bleeding. Perforation and obstruction occurred uncommonly. Overall, upper GI events occurred less frequently in the etoricoxib group (n=176/17,412) than they did in the diclofenac group (n=246/17,289) (hazard ratio (HR) 0.69; 95% confidence interval (CI), 0.57-0.83; p=0.0001); however, there was no difference in complicated upper GI events (HR 0.91; 95% CI, 0.67-1.24; p=0.561). There were significantly fewer uncomplicated upper GI events in the etoricoxib group (n=98/17,412) vs the diclofenac group (n=164/17,289) (HR 0.57; 95% CI, 0.45-0.74, p less than 0.0001), and the rates of uncomplicated ulcers were 0.35 (95% CI, 0.28-0.43) per 100 patient-years for etoricoxib vs 0.63 (95% CI, 0.54-0.74) per 100 patient-years for diclofenac. Subgroup analyses were also conducted among patients using proton-pump inhibitor (PPI) or low-dose aspirin concurrently for at least 75% of the study period. Patients taking PPIs with etoricoxib experienced significantly fewer upper GI events (n=68/6950) than the patients taking PPIs with diclofenac (n=106/6906) (HR 0.62; 95% CI, 0.45-0.83). While there were no differences between these subgroups in complicated GI events (HR 0.72; 95% CI, 0.42-1.22), there were significantly fewer uncomplicated upper GI events in patients taking PPIs with etoricoxib (n=44/6950) than in patients taking PPIs with diclofenac (n=74/6906) (HR 0.57; 95% CI, 0.39-0.83). Similarly, in patients using low-dose aspirin concurrently, there was no difference in complicated upper GI events between patients in the etoricoxib (n=50/5752) and diclofenac groups (n=52/5680) (HR 0.93; 95% CI, 0.63-1.36). However, there were significantly fewer uncomplicated upper GI events in patients in the diclofenac group (n=50/5752) vs the etoricoxib group (n=72/5680) (HR 0.67; 95% CI, 0.47-0.96). Overall, the discontinuation rates due to any GI adverse event were 3.92 per 100 patient-years for etoricoxib and 5.69 per 100 patient-years for diclofenac (HR 0.69; 95% CI, 0.64-0.75; p less than 0.0001) [14].

2) In pharmacokinetic studies, NAUSEA, VOMITING, DIARRHEA, HEARTBURN, TASTE DISTURBANCES, DECREASED APPETITE and FLATULENCE have been reported occasionally [13][15].

3) In a double-blind study in healthy subjects (n=62), fecal blood loss with etoricoxib 120 milligrams (mg) once daily was similar to that of placebo and less than that observed with ibuprofen 800 mg three times daily [16].

3.3.9 Neurologic Effects

3.3.9.A Central nervous system finding

1) In pharmacokinetic studies, HEADACHE, DIZZINESS, FATIGUE, and INSC occasionally [13].

3.5 Drug Interactions

3.5.1 Drug-Drug Combinations

Desvenlafaxine

Duloxetine

Milnacipran

Venlafaxine

3.5.1.A Desvenlafaxine

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and norepinephrine reuptake inhibitors (such as desvenlafaxine) and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages[18].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When desvenlafaxine and a nonsteroidal antiinflammatory agent are given concurrently, monitor patient for signs of increased bleeding[18].
7) Probable Mechanism: unknown

3.5.1.B Duloxetine

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and norepinephrine reuptake inhibitors (such as duloxetine) and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages[19].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When duloxetine and a nonsteroidal antiinflammatory agent are given concurrently, monitor patient for signs of increased bleeding[19].
7) Probable Mechanism: unknown

3.5.1.C Milnacipran

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of selective serotonin and norepinephrine reuptake inhibitors (such as milnacipran) and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages[17].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When milnacipran and an NSAID are given concurrently, monitor patient for signs of increased bleeding[17].
7) Probable Mechanism: unknown

3.5.1.D Venlafaxine

1) Interaction Effect: an increased risk of bleeding
2) Summary: The release of serotonin by platelets is important for maintaining hemostasis. Case-control and cohort studies have shown that the combined use of SSRIs (such as venlafaxine) and NSAIDs has been associated with an increased risk of bleeding. Bleeding events have included epistaxis, ecchymosis, hematoma, petechiae, and life-threatening hemorrhages[20].
3) Severity: moderate
4) Onset: unspecified
5) Substantiation: probable
6) Clinical Management: When venlafaxine and a nonsteroidal antiinflammat

monitor patient for signs of increased bleeding[20].
7) Probable Mechanism: unknown

4.0 Clinical Applications

Monitoring Parameters

Place In Therapy

Mechanism of Action / Pharmacology

Therapeutic Uses

Comparative Efficacy / Evaluation With Other Therapies

4.1 Monitoring Parameters

A) Therapeutic
1) Physical Findings
a) Osteoarthritis/Rheumatoid Arthritis
1) Clinical symptoms (eg, improvement of pain, stiffness, mobility, swollen/tender joints)
2) Quality of life assessment
B) Toxic
1) Laboratory Parameters
a) Renal function tests, liver function tests, hematocrit, hemoglobin, and serum electrolytes during chronic therapy
2) Physical Findings
a) Blood pressure in patients with cardiovascular disease
b) Upper gastrointestinal tests are suggested in patients with persistent dyspepsia
c) Signs of persistent and/or severe gastrointestinal toxicity (eg, continuous indigestion, nausea, or cramps; hematemesis)

4.3 Place In Therapy

A) The selective COX-2 inhibitory effects of etoricoxib are an advantage over nonselective nonsteroidal antiinflammatory agents primarily with regard to gastrointestinal toxicity. Lack of platelet effects is also an advantage. However, there is no evidence that renal events are reduced by any selective COX-2 inhibitor. In general, etoricoxib would be preferred over nonselective agents for treatment of arthritis patients with known risk factors for ulceration or bleeding, particularly the elderly. However, clarification of the risk of thrombotic events with this agent is required before it can be recommended. Comparisons with other selective COX-2 inhibitors (eg, rofecoxib, celecoxib) with respect to efficacy and noncardiovascular toxicity are also needed to establish its place in therapy.
B) Etoricoxib has not been investigated in the treatment of dysmenorrhea or postoperative pain following major surgery.

4.4 Mechanism of Action / Pharmacology

A) MECHANISM OF ACTION
1) Etoricoxib is a nonsteroidal antiinflammatory agent (dipyridinyl derivative) for oral administration. It is a selective inhibitor of cyclooxygenase-2 (COX-2) [29][25].
2) The COX-1 isoenzyme is constitutively expressed in most tissues, and is particularly involved in prostaglandin synthesis in kidneys, platelets, and gastric mucosa; products of COX-1 appear cytoprotective, and inhibition of this isoform has been associated with antiplatelet and gastrointestinal toxicity. The inducible COX-2 isoform is expressed at sites of inflammation, and its inhibition is considered responsible for analgesic and antiinflammatory properties of nonsteroidal antiinflammatory agents [25][24][27]. The COX-1-sparing effects of selective COX-2 inhibitors suggest they may be as effective as nonselective inhibitors of both COX-1 and COX-2 (ie, naproxen, ibuprofen, ketorolac) in treating pain and inflammation with a reduced propensity for hematologic and gastrointestinal toxicity. This benefit has been observed in some comparative studies with the oral COX-2 inhibitors celecoxib and rofecoxib; however, GI bleeding has occurred in some patients with both of these agents. It remains unclear if any COX-2 inhibitor can provide a clinically significant advantage over nonselective agents with regard to renal toxicity.
3) In vitro data indicate that etoricoxib is a potent and highly selective COX-2 inhibitor [29][25]. Based on the ratio of concentrations required for 50% inhibition of enzyme activity (COX-1/COX-2), the selectivity ratio for COX-2 in human whole blood assays was 106 for etoricoxib compared to 30 for valdecoxib, 35 for rofecoxib, 7.6 for celecoxib, 3 for diclofenac, 2.4 for etodolac, and less than 1 for ibuprofen, piroxicam, and indomethacin [29].
4) In a double-blind study in healthy subjects (n=62), fecal blood loss with etoricox
was similar to that of placebo and less than that observed with ibuprofen 800 mg t

B) REVIEW ARTICLES

1) Etoricoxib synthesis, pharmacology, and clinical studies [25].

4.5 Therapeutic Uses

Ankylosing spondylitis

Dental pain

Dysmenorrhea

Osteoarthritis

Rheumatoid arthritis

4.5.A Ankylosing spondylitis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class IIb
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

In a double-blind, parallel-group, 52-week study, etoricoxib therapy significantly improved patient's assessment of spine pain, disease activity, and Bath Ankylosing Spondylitis Functional Index (BASFI) on visual analog scale (VAS) compared with naproxen in patients with Ankylosing Spondylitis (AS) [1]

3) Adult:

a) In a double-blind, parallel-group, 52-week study, etoricoxib therapy significantly improved patient's assessment on visual analog scale (VAS) of spine pain, disease activity, and Bath Ankylosing Spondylitis Functional Index (BASFI) compared with naproxen in patients with Ankylosing Spondylitis (AS). Patients with AS (diagnosed using modified New York criteria), routine use of nonsteroidal antiinflammatory drugs (NSAIDs) and nonstudy antirheumatic therapy, and worsening spine pain (using patient's assessment of spine pain on VAS) following the prestudy washout period for NSAIDs were eligible for enrollment. Patients were excluded if they received corticosteroid therapy within 1 month of study entry, analgesics (other than acetaminophen) within 3 days before or 6 weeks after study entry, or nonstudy NSAIDs (except low dose (100 mg or less) aspirin) or selective cyclooxygenase 2 (COX-2) inhibitors. In part 1, patients (n=387; mean age, 43.6 +/- 11.9 years) were randomized 1:1:1:1 to receive etoricoxib 90 milligrams (mg) or 120 mg daily, naproxen 500 mg twice daily, or placebo for 6 weeks. In part 2 (46 weeks), patients (n=374) remained in their respective groups; however, patients who received placebo in part 1 were randomized 1:1:1 to receive etoricoxib 90 mg or 120 mg daily or naproxen 500 mg twice daily. After 6 weeks (part 1), patients receiving etoricoxib 90 mg or 120 mg (combined results) experienced greater score improvements (compared with baseline) in the three primary endpoints compared with patients receiving placebo (patient's assessment of spine pain, -41.5 +/- 1.6 vs -12.6 +/- 2.3; p less than 0.001; patient's assessment of disease activity, -27.3 +/- 1.5 vs -3.4 +/- 2.2; p less than 0.001; BASFI, -19.3 +/- 1.3 vs -4 +/- 1.9; p less than 0.001). The combined results of etoricoxib 90 mg or 120 mg were also greater compared with naproxen (patient's assessment of spine pain, -41.5 +/- 1.6 vs -33.7 +/- 2.3; p less than 0.01; patient's assessment of disease activity, -27.3 +/- 1.5 vs -20.9 +/- 2.1; p less than 0.05; BASFI, -19.3 +/- 1.3 vs -14.6 +/- 1.8; p less than 0.05). Similarly, after a total of 52 weeks patients receiving etoricoxib 90 mg or 120 mg (combined results) continued to have increased score improvements (compared with baseline) in the three primary endpoints compared with patients receiving naproxen (patient's assessment of spine pain, -43.7 +/- 1.6 vs -35.4 +/- 2.3; p less than 0.01; patient's assessment of disease activity, -29.8 +/- 1.6 vs -22.6 +/- 2.2; p less than 0.01; BASFI, -22 +/- 1.4 vs -16.1 +/- 1.9; p less than 0.05). Commonly (greater than 7.5% in any group) reported adverse events that occurred more often in the etoricoxib 90 mg and 120 mg group compared with the naproxen group over the 52-week study included upper respiratory tract infection (10.9% and 19.3% vs 11.5%), dyspepsia (15.2% and 3.6% vs 2.6%), diarrhea (13% and 7.2% vs 6.4%), and headache (10.9% and 9.6% vs 5.1%). Serious cardiovascular thrombotic adverse events occurred in 3.2% and 0.8% of patients who received etoricoxib 90 mg and 120 mg compared with 0% of patients who received naproxen [1].

4.5.B Dental pain

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATING

2) Summary:

Single oral doses of 120 milligrams (mg) have been effective and comparable to naproxen 550 mg [2]

3) Adult:

a) Single oral doses of 120 milligrams (mg) have been effective in treating acute pain following dental surgery (removal of at least 2 third molars) in double-blind studies; pain relief was not greater with doses of 180 or 240 mg [3][2][4]. In these studies, a duration of action of at least 24 hours was reported with 120-mg doses. Efficacy has been similar to ibuprofen and naproxen [3][2].

b) In a placebo-controlled, double-blind study involving 200 patients, the single-dose analgesic efficacy of etoricoxib 120 mg was comparable to that of naproxen 550 mg and greater than that of acetaminophen/codeine 600/60 mg. The least squares means for total pain relief over 8 hours (TOTPAR8), the primary endpoint, were 20.1, 20.6, 10.7, and 4.6 units for etoricoxib, naproxen, acetaminophen/codeine, and placebo, respectively. Onset of action was similar with all three active regimens (about 30 minutes); durations of analgesia were longer than 24 hours for etoricoxib, approximately 22 hours for naproxen, 5.2 hours for acetaminophen/codeine, and 2 hours for placebo [2].

4.5.C Dysmenorrhea

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

More effective than placebo and as effective as naproxen sodium for reducing pain of dysmenorrhea [5]

3) Adult:

a) Etoricoxib was more effective than placebo and as effective as naproxen sodium for relieving pain of dysmenorrhea. In a randomized, double-blind, controlled crossover trial, women with moderate or severe dysmenorrhea in at least 4 of their last 6 menstrual cycles were given single doses of etoricoxib 120 milligrams (mg), naproxen sodium 550 mg, or placebo to take at onset of pain at each menstrual cycle over 3 months. Each woman was to take all 3 treatments, in random order--one each month. Scores for relief of pain over the first 8 hours were higher for etoricoxib (20 units) and naproxen sodium (21.5 units) than for placebo (12.6 units (p less than 0.001 for each in comparison to placebo). There was no difference between etoricoxib and naproxen sodium. Median times to onset of analgesic activity were 1.5 hours (hr) for etoricoxib, 1 hr for naproxen sodium, and 2 hr for placebo. Thirteen percent of women required rescue medication after taking etoricoxib, 44% after placebo, and 19% after naproxen sodium. Duration of effect was longer than 24 hr for each treatment [5].

4.5.D Osteoarthritis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Once-daily dosing effective for up to 14 weeks in a placebo-controlled study

Shown to be as effective as naproxen with possibly fewer side effects

3) Adult:

a) For treatment of osteoarthritis of the knee or hip, a 12-week course of oral etoricoxib was well tolerated and demonstrated similar efficacy to naproxen (active comparator) and significant superiority to placebo, based a double-blind, multicenter trial (n=501). Patients were randomized to placebo (n=56), etoricoxib 60 milligrams (mg) once daily in the morning (n=224), or naproxen 500 mg twice daily (morning & evening) (n=221). Compared with placebo, etoricoxib and naproxen provided significantly greater improvement (p less than 0.001) as measured by the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) pain subscale, the WOMAC physical function subscale, and the patient global assessment of disease status. On these primary endpoints, no significant differences were found between etoricoxib and naproxen. Response to therapy was rapid for both active treatments, with a statistically significant difference from placebo appearing by day 2. Also, the WOMAC score for night pain and stiffness upon first awakening was significantly better for etoricoxib than placebo (p=0.009), indicating sustained response over the 24-hour dosing int
confirmed the greater (and similar) efficacy of both active agents over placebo
etoricoxib and naproxen were epigastric discomfort, heartburn, diarrhea, and

hypertension was reported in 7.6%, 3.2%, and 8.9% of the etoricoxib, naproxen, and control groups, respectively. Five patients experienced upper gastrointestinal perforations, ulcers, or bleeding events, all were in the naproxen group; no thrombotic cardiovascular events occurred in any group. Rates of discontinuation due to adverse events were similar across all groups, with significantly fewer in the etoricoxib and naproxen groups withdrawing due to lack of efficacy (p less than or equal 0.028) [6].

b) In a 6-week blinded study (n=617), etoricoxib 5, 10, 30, 60, or 90 milligrams (mg) once daily was statistically superior to placebo in the treatment of osteoarthritis of the knee, based on changes in the WOMAC pain subscale and patient and physician global assessments. Dose-related efficacy was seen up to 60 mg daily; doses of 30 mg were about half as effective as 60 or 90 mg. No significant dose-related trends for adverse events were observed [7]. An 8-week extension of this study demonstrated sustained efficacy and good tolerability [4].

4.5.E Rheumatoid arthritis

1) Overview

FDA Approval: Adult, no; Pediatric, no
Efficacy: Adult, Evidence favors efficacy
Recommendation: Adult, Class III
Strength of Evidence: Adult, Category B
See Drug Consult reference: RECOMMENDATION AND EVIDENCE RATINGS

2) Summary:

Once-daily dosing effective in one trial [8]

3) Adult:

a) Oral etoricoxib 90 or 120 milligrams (mg) once daily was effective in treating rheumatoid arthritis in an 8-week, double-blind, placebo-controlled study (n=581). With these doses, the drug was significantly superior to placebo (intent-to-treat analysis) on patient and investigator global assessments of disease activity (primary endpoints), patient assessment of pain, and the Stanford Health Assessment Questionnaire Disability Index [8]. Lower doses of 10 and 60 mg etoricoxib were also evaluated in this study; relative efficacy data were not presented.

4.6 Comparative Efficacy / Evaluation With Other Therapies

Acetaminophen/Codeine Phosphate

Diclofenac

Ibuprofen

Naproxen

4.6.A Acetaminophen/Codeine Phosphate

4.6.A.1 Dental pain

a) In a placebo-controlled, double-blind study involving 200 patients, the single-dose analgesic efficacy of etoricoxib 120 mg was comparable to that of naproxen 550 mg and greater than that of acetaminophen/codeine 600/60 mg. The least squares means for total pain relief over 8 hours (TOTPAR8), the primary endpoint, were 20.1, 20.6, 10.7, and 4.6 units for etoricoxib, naproxen, acetaminophen/codeine, and placebo, respectively. Onset of action was similar with all three active regimens (about 30 minutes); durations of analgesia were longer than 24 hours for etoricoxib, approximately 22 hours for naproxen, 5.2 hours for acetaminophen/codeine, and 2 hours for placebo [33].

4.6.B Diclofenac

1) Adverse Effects

a) According to results from the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) program, there were significantly fewer upper gastrointestinal (GI) events and uncomplicated GI events with etoricoxib than with diclofenac in patients with osteoarthritis and rheumatoid arthritis; however, there were no significant differences in complicated GI events between the groups. The MEDAL program (n=34,701) was prospectively designed to pool data from 3 randomized, double-blind clinical trials: MEDAL (n=23,504), etoricoxib vs diclofenac sodium GI tolerability and effectiveness study (EDGE; n=7111), and EDGE II (n=4086). The patients were randomly assigned etoricoxib 60 or 90 mg orally daily (n=17,412) or diclofenac 150 mg orally daily (n=17,289). The most common GI events were uncomplicated ulcer and comp
GI bleeding. Perforation and obstruction occurred uncommonly. Overall, uppe
frequently in the etoricoxib group (n=176/17,412) than they did in the diclofen

ratio (HR) 0.69; 95% confidence interval (CI), 0.57-0.83; p=0.0001); however, there was no difference in complicated upper GI events (HR 0.91; 95% CI, 0.67-1.24; p=0.561). There were significantly fewer uncomplicated upper GI events in the etoricoxib group (n=98/17,412) vs the diclofenac group (n=164/17,289) (HR 0.57; 95% CI, 0.45-0.74, p less than 0.0001), and the rates of uncomplicated ulcers were 0.35 (95% CI, 0.28-0.43) per 100 patient-years for etoricoxib vs 0.63 (95% CI, 0.54-0.74) per 100 patient-years for diclofenac. Subgroup analyses were also conducted among patients using proton-pump inhibitor (PPI) or low-dose aspirin concurrently for at least 75% of the study period. Patients taking PPIs with etoricoxib experienced significantly fewer upper GI events (n=68/6950) than the patients taking PPIs with diclofenac (n=106/6906) (HR 0.62; 95% CI, 0.45-0.83). While there were no differences between these subgroups in complicated GI events (HR 0.72; 95% CI, 0.42-1.22), there were significantly fewer uncomplicated upper GI events in patients taking PPIs with etoricoxib (n=44/6950) than in patients taking PPIs with diclofenac (n=74/6906) (HR 0.57; 95% CI, 0.39-0.83). Similarly, in patients using low-dose aspirin concurrently, there was no difference in complicated upper GI events between patients in the etoricoxib (n=50/5752) and diclofenac groups (n=52/5680) (HR 0.93; 95% CI, 0.63-1.36). However, there were significantly fewer uncomplicated upper GI events in patients in the diclofenac group (n=50/5752) vs the etoricoxib group (n=72/5680) (HR 0.67; 95% CI, 0.47-0.96). Overall, the discontinuation rates due to any GI adverse event were 3.92 per 100 patient-years for etoricoxib and 5.69 per 100 patient-years for diclofenac (HR 0.69; 95% CI, 0.64-0.75; p less than 0.0001) [14].

b) A randomized, double-blind clinical trial (Etoricoxib Diclofenac Gastrointestinal Evaluation (EDGE) study; unpublished study results) suggested that etoricoxib and diclofenac had comparable rates of thrombotic cardiovascular events. In this randomized, double-blind clinical trial, osteoarthritis patients received either etoricoxib 90 milligrams (mg) once daily (n=3593) or diclofenac sodium 50 mg three times daily (n=3518) for up to 16.5 months (mean duration 9 months). Patients included those with history of an upper gastrointestinal event (4%), high-risk for cardiovascular disease (37%), current diagnosis of hypertension (45%), and use of low-dose aspirin (28%). Concomitant therapy with gastroprotective agents and low-dose aspirin were permitted during the study. The primary study endpoint was gastrointestinal tolerability; it is unclear from the manufacturer's report if the study was adequately powered to detect a difference in cardiovascular events. Etoricoxib significantly reduced the rate of treatment discontinuation due to gastrointestinal adverse events. The rates for myocardial infarction within 14 days of treatment discontinuation were 0.68 per 100 patient years for etoricoxib and 0.42 per 100 patient years for diclofenac; the rates for stroke were 0.15 and 0.23 for etoricoxib and diclofenac, respectively. Withdrawal from the study due to hypertension-related adverse events occurred significantly more often in the etoricoxib group (2.3%) compared to the diclofenac group (0.7%; p less than 0.001). The relative risk of thrombotic cardiovascular events for etoricoxib compared to diclofenac was 1.07 (95% confidence interval (CI), 0.65 to 1.74) for events within 14 days after treatment discontinuation and 1.02 (95% CI, 0.64 to 1.62) for events within 28 days of treatment discontinuation [36][37]. The short duration of therapy (mean, 9 months) is a limitation of these study results; for rofecoxib, another COX-2 inhibitor, increases in thrombotic cardiovascular events were not observed until at least 18 months of therapy (Bresalier et al, 2004 [38].

4.6.C Ibuprofen

4.6.C.1 Dental pain

a) The analgesic activity of etoricoxib 120 to 240 milligrams (mg) was similar to that of ibuprofen 400 mg in a single-dose study involving 398 dental surgery patients. Onset of action was also similar (about 25 minutes), whereas duration of analgesia was longer with etoricoxib (greater than 24 hours versus 10 hours) [35]. In this study, doses of etoricoxib exceeding 120 mg did not provide greater pain relief.

4.6.C.2 Adverse Effects

a) In a double-blind study in healthy subjects (n=62), fecal blood loss with etoricoxib 120 milligrams (mg) once daily was similar to that of placebo and less than that observed with ibuprofen 800 mg three times daily [34].

4.6.D Naproxen

Dental surgical procedure - Postoperative pain

Rheumatoid arthritis

4.6.D.1 Dental surgical procedure - Postoperative pain

a) In a placebo-controlled, double-blind study involving 200 patients, the single-dose analgesic efficacy of etoricoxib 120 mg was comparable to that of naproxen 550 mg and greater than that of acetaminophen/codeine 600/60 mg. The least squares means for total pain relief over 8 hours (TOTPAR8), the primary endpoint, were 20.1, 20.6, 10.7, and 4.6 units for etoricoxib, naproxen, acetaminophen/codeine, and placebo, respectively. Onset of action was similar with all three active regimens (about 30 minutes); durations of analgesia were longer than 24 hours for etoricoxib, approximately 22 hours for naproxen, 5.2 hours for acetaminophen/codeine, and 2 hours for placebo [31].

4.6.D.2 Rheumatoid arthritis

a) Etoricoxib 90 milligrams (mg) once daily was similarly effective as naproxen 500 mg twice daily and both were superior to placebo during a 12-week evaluation in patients with rheumatoid arthritis. Concurrent medications (except for TNF inhibitors or other NSAIDs) were allowed, and nearly 60% continued on steroids, 80% on DMARDs, and 60% on methotrexate. Global assessment at baseline was no better than "fair" with either prolonged morning stiffness, a VAS score greater than 40 for patient assessed pain, with a recent increase in pain score of at least 10 mm. ACR outcome measures were used, with 4 specified endpoints of tender joint count, swollen joint count, patient global assessment of disease activity, and investigator global assessment. Patient assessment of pain, activities of daily living, and the ACR20 response criteria were secondary measures. Approximately 350 patients each received active drug against 180 placebo controls. Dropouts for lack of effect were twice as common among controls (25% versus 12%). When expressed as change from baseline, disease activity scores (VAS) improved 10 mm for active drug; investigator global assessment (4-point scale) improved by 0.5 points (from baseline 2.6); tender joint count was down an average of 3.5 (baseline 29); and swollen joint count was down 1.4 (19 baseline). There were no changes in controls [32].

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