PHL-MK0663-T-052010

PRODUCT CIRCULAR

ETORICOXIB

ARCOXIA™ / ARCOXIA™ Ac

Tablets
COX-2 Specific Inhibitor

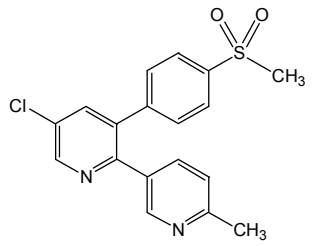
NAME AND STRENGTH OF ACTIVE INGREDIENT

Each tablet of ETORICOXIB (ARCOXIA) for oral administration contains either 30, 60, 90 or 120 mg of etoricoxib.

PRODUCT DESCRIPTION

ETORICOXIB (ARCOXIA) is a member of a class of arthritis/analgesia medications called Coxibs. ETORICOXIB (ARCOXIA) is a highly selective inhibitor of cyclooxygenase-2 (COX-2).

ETORICOXIB (ARCOXIA) tablets contain etoricoxib, which is described chemically as 5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine. The empirical formula is $C_{18}H_{15}ClN_2O_2S$. The molecular weight is 358.84. The structural formula is:



Etoricoxib is a white to off-white powder. Etoricoxib is freely soluble in methanol, tetrahydrofuran, dimethyl sulfoxide, methyl ethyl ketone, dimethyl formamide, and chloroform. Etoricoxib is soluble in isopropyl acetate, ethanol and toluene, sparingly soluble in 2-propanol, and practically insoluble in water.

PHARMACOKINETICS

Absorption

Orally administered etoricoxib is well absorbed. The mean oral bioavailability is approximately 100%. Following 120-mg once-daily dosing to steady state, the peak plasma concentration (geometric mean C_{max} = 3.6 mcg/mL) was observed at approximately 1 hour (T_{max}) after administration to fasted adults. The geometric mean $AUC_{0\text{-}24hr}$ was 37.8 mcg•hr/mL. The pharmacokinetics of etoricoxib are linear across the clinical dose range.

A standard meal had no clinically meaningful effect on the extent or rate of absorption of a dose of etoricoxib 120 mg. In clinical trials, etoricoxib was administered without regard to food.

The pharmacokinetics of etoricoxib in 12 healthy subjects were similar (comparable AUC, C_{max} within approximately 20%) when administered alone, with a magnesium/aluminum hydroxide antacid, or a calcium carbonate antacid (approximately 50 mEq acid-neutralizing capacity).

Distribution

Etoricoxib is approximately 92% bound to human plasma protein over the range of concentrations of 0.05 to 5 mcg/mL. The volume of distribution at steady state (V_{dss}) is approximately 120 L in humans.

Etoricoxib crosses the placenta in rats and rabbits, and the blood-brain barrier in rats.

Metabolism

Etoricoxib is extensively metabolized with <1% of a dose recovered in urine as the parent drug. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalyzed by cytochrome P450 (CYP) enzymes.

Five metabolites have been identified in man. The principal metabolite is the 6'-carboxylic acid derivative of etoricoxib formed by further oxidation of the 6'-hydroxymethyl derivative. These principal metabolites either demonstrate no measurable activity or are only weakly active as COX-2 inhibitors. None of these metabolites inhibit COX-1.

Elimination

Following administration of a single 25-mg radiolabeled intravenous dose of etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in feces, mostly as metabolites. Less than 2% was recovered as unchanged drug.

Elimination of etoricoxib occurs almost exclusively through metabolism followed by renal excretion. Steady state concentrations of etoricoxib are reached within seven days of once-daily administration of 120 mg, with an accumulation ratio of approximately 2, corresponding to an accumulation half-life of approximately 22 hours. The plasma clearance is estimated to be approximately 50 mL/min.

Characteristics in Patients (Special Populations)

Gender
The pharmacokinetics of etoricoxib are similar between men and women. (See RECOMMENDED DOSE.)

Elderly
Pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young. No dosage adjustment is necessary for elderly patients. (See RECOMMENDED DOSE.)

Race
There is no clinically important effect of race on the pharmacokinetics of etoricoxib. (See RECOMMENDED DOSE.)

Hepatic Insufficiency
Patients with mild hepatic insufficiency (Child-Pugh score 5-6) administered etoricoxib 60 mg once daily had an approximately 16% higher mean AUC as compared to healthy subjects given the same regimen. Patients with moderate hepatic insufficiency (Child-Pugh score 7-9) administered etoricoxib 60 mg ***every other day*** had similar mean AUC to the healthy subjects given etoricoxib 60 mg once daily; etoricoxib 30 mg once daily has not been studied in this population. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). (See RECOMMENDED DOSE, *Hepatic Insufficiency.*)

Renal Insufficiency
The pharmacokinetics of a single dose of etoricoxib 120 mg in patients with moderate-to-severe renal insufficiency and patients with end-stage renal disease on hemodialysis were not significantly different from those in healthy subjects. Hemodialysis contributed negligibly to elimination (dialysis clearance approximately 50 mL/min).

Pediatric Patients
The pharmacokinetics of etoricoxib in pediatric patients (<12 years of age) have not been studied.

In a pharmacokinetic study (N=16) conducted in adolescents (aged 12 to 17) the pharmacokinetics in adolescents weighing 40 to 60 kg given etoricoxib 60 mg once daily and in adolescents >60 kg given etoricoxib 90 mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90 mg once daily. Safety and effectiveness of etoricoxib in pediatric patients have not been established.

Drug Interactions with additional pharmacokinetic data

The main pathway of etoricoxib biotransformation is CYP-dependent oxidation to produce 6'-hydroxymethyl etoricoxib, which can undergo further metabolism to the corresponding carboxylic acid or *O*-glucuronide. *In vitro* data indicate that CYP3A4 plays a major role (approximately 60%) in the hydroxylation of etoricoxib and that the remainder of the activity (approximately 40%) is shared among CYP2C9, 1A2, 2C19, and 2D6. Administration of a potent inhibitor of CYP3A4 (ketoconazole) did not increase etoricoxib plasma concentrations to a clinically meaningful extent (approximate 43% increase in AUC). Administration of a potent inducer of CYP enzymes (rifampin) produced a 65% decrease in etoricoxib plasma AUC.

The potential for etoricoxib to inhibit or induce CYP3A4 activity was investigated in human studies using the intravenous erythromycin breath test. Compared to placebo, etoricoxib (120 mg daily for 11 days) did not produce any significant effect on erythromycin N-demethylation, indicating no effect on hepatic CYP3A4 activity. Based on *in vitro* studies, etoricoxib does not inhibit cytochromes P450 1A2, 2C9, 2C19, 2D6, or 2E1.

INDICATIONS

ETORICOXIB (ARCOXIA) is indicated for:

- Acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA)
- Treatment of ankylosing spondylitis (AS)
- Treatment of acute gouty arthritis
- Relief of acute pain
- Treatment of primary dysmenorrhea.

The decision to prescribe a selective COX-2 inhibitor should be based on an assessment of the individual patient's overall risks (see WARNINGS AND PRECAUTIONS).

RECOMMENDED DOSE

ETORICOXIB (ARCOXIA) is administered orally. ETORICOXIB (ARCOXIA) may be taken with or without food.

Arthritis
Osteoarthritis
The recommended dose is 30mg or 60 mg once daily.

Rheumatoid Arthritis
The recommended dose is 90 mg once daily.

Ankylosing Spondylitis
The recommended dose is 90 mg once daily.

Acute Gouty Arthritis
The recommended dose is 120 mg once daily. ETORICOXIB (ARCOXIA) 120 mg should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.

Analgesia
Acute Pain and Primary Dysmenorrhea
The recommended dose is 120 mg once daily. ETORICOXIB (ARCOXIA) 120 mg should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.

Doses greater than those recommended for each indication have either not demonstrated additional efficacy or have not been studied. Therefore:

The dose for OA should not exceed 60 mg daily.
The dose for RA should not exceed 90 mg daily.
The dose for ankylosing spondylitis should not exceed 90 mg daily.
The dose for acute gout should not exceed 120 mg daily.
The dose for acute pain and primary dysmenorrhea should not exceed 120 mg daily.

As the cardiovascular risks of selective COX-2 inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically. (See WARNINGS AND PRECAUTIONS)

Elderly, Gender, Race
No dosage adjustment in ETORICOXIB (ARCOXIA) is necessary for the elderly or based on gender or race.

Hepatic Insufficiency

In patients with mild hepatic insufficiency (Child-Pugh score 5-6), a dose of 60 mg once daily should not be exceeded. In patients with moderate hepatic insufficiency (Child-Pugh score 7-9), the dose should be reduced; a dose of 60 mg ***every other day*** should not be exceeded, administration of 30 mg once daily can also be considered. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). (See WARNINGS AND PRECAUTIONS.)

Renal Insufficiency

In patients with advanced renal disease (creatinine clearance <30 mL/min), treatment with ETORICOXIB (ARCOXIA) is not recommended. No dosage adjustment is necessary for patients with lesser degrees of renal insufficiency (creatinine clearance ≥30 mL/min). (See WARNINGS AND PRECAUTIONS.)

MODE OF ADMINISTRATION

ETORICOXIB (ARCOXIA) is administered orally. ETORICOXIB (ARCOXIA) may be taken with or without food.

CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

Active peptic ulceration or active gastro-intestinal (GI) bleeding.

Patients who have experienced bronchospasm, acute rhinitis, nasal polyps, angioneurotic oedema, urticaria, or allergic-type reactions after taking acetylsalicylic acid or NSAIDS including COX-2 (cyclooxygenase-2) inhibitors.

Pregnancy and lactation.

Severe hepatic dysfunction (serum albumin <25g/l or Child-Pugh score≥10).

Estimated renal creatinine clearance <30 mL/min.

Children and adolescents under 16 years of age.

Inflammatory bowel disease.

Congestive heart failure (NYHA II-IV).

Patients with hypertension whose blood pressure has not been adequately controlled.

Established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease.

WARNINGS AND PRECAUTIONS

Clinical trials suggest that the selective COX-2 inhibitor class of drugs may be associated with an increased risk of thrombotic events (especially MI and stroke), relative to placebo and some NSAIDs (naproxen). As the cardiovascular risks of selective COX-2 inhibitors may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.

Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidemia, diabetes mellitus, smoking) should only be treated with etoricoxib after careful consideration.

Selective COX-2 inhibitors are not a substitute for aspirin for cardiovascular prophylaxis because of their lack of effect on platelets. Because etoricoxib, a member of this class, does not inhibit platelet aggregation, antiplatelet therapies should not be discontinued.

There is a further increase in the risk of gastrointestinal adverse effects (gastrointestinal ulceration or other gastrointestinal complications) for etoricoxib, other selective COX-2 inhibitors and NSAIDs, when taken concomitantly with acetylsalicylic acid (even at low doses). The relative difference in gastrointestinal safety between selective COX-2 inhibitors + acetylsalicylic acid vs. NSAIDs + acetylsalicylic acid has not been adequately evaluated in long-term clinical trials.

Long-term administration of NSAIDs has resulted in renal papillary necrosis and other renal injury. Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of ETORICOXIB (ARCOXIA) may cause a reduction in prostaglandin formation and, secondarily, in renal blood flow, and thereby impair renal function. Patients at greatest risk of this response are those with pre-existing significantly impaired renal function, uncompensated heart failure, or cirrhosis. Monitoring of renal function in such patients should be considered.
Caution should be used when initiating treatment with ETORICOXIB (ARCOXIA) in patients with considerable dehydration. It is advisable to rehydrate patients prior to starting therapy with ETORICOXIB (ARCOXIA).

As with other drugs known to inhibit prostaglandin synthesis, fluid retention, edema and hypertension have been observed in some patients taking ETORICOXIB (ARCOXIA). The possibility of fluid retention, edema or hypertension should be taken into consideration when ETORICOXIB (ARCOXIA) is used in patients with pre-existing edema, hypertension, or heart failure. All Nonsteroidal Antiinflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. (see UNDESIRABLE EFFECTS.)Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, special attention should be paid to blood pressure monitoring during treatment with etoricoxib. If blood pressure rises significantly, alternative treatment should be considered.

Physicians should be aware that individual patients may develop upper gastrointestinal (GI) ulcers/ulcer complications irrespective of treatment. Although the risk of GI toxicity is not eliminated with ETORICOXIB (ARCOXIA), the results of the MEDAL Program demonstrate that in patients treated with ETORICOXIB (ARCOXIA), the risk of GI toxicity with ETORICOXIB (ARCOXIA) 60 mg or 90 mg once daily is significantly less than with diclofenac 150 mg daily. In clinical studies with ibuprofen and naproxen, the risk of endoscopically detected upper GI ulcers was lower in patients treated with ETORICOXIB (ARCOXIA) 120 mg once daily than in patients treated with non-selective NSAIDs. While the risk of endoscopically detected ulcers was low in patients treated with ETORICOXIB (ARCOXIA) 120 mg it was higher than in patients treated with placebo. Upper GI ulcers/ulcer complications have occurred in patients treated with ETORICOXIB (ARCOXIA). These events can occur at any time during use and without warning symptoms. Independent of treatment, patients with a prior history of GI perforation, ulcers and bleeding (PUB) and patients greater than 65 years of age are known to be at a higher risk for a PUB.

Elevations of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (approximately three or more times the upper limit of normal) have been reported in approximately 1% of patients in clinical trials treated for up to one year with ETORICOXIB (ARCOXIA) 30, 60 and 90 mg daily. In active comparator portions of clinical trials, the incidence of elevated AST and/or ALT in patients treated with ETORICOXIB (ARCOXIA) 60 and 90 mg daily was similar to that of patients treated with naproxen 1000 mg daily, but notably less than the incidence in the diclofenac 150 mg daily group. These elevations resolved in patients treated with ETORICOXIB (ARCOXIA), with approximately half resolving while

patients remained on therapy. In controlled clinical trials of ETORICOXIB (ARCOXIA) 30 mg daily versus ibuprofen 2400 mg daily or celecoxib 200 mg daily, the incidence of elevations of ALT or AST was similar.

A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver function test has occurred, should be evaluated for persistently abnormal liver function tests. If persistently abnormal liver function tests (three times the upper limit of normal) are detected, ETORICOXIB (ARCOXIA) should be discontinued.

When using etoricoxib in the elderly and in patients with renal, hepatic, or cardiac dysfunction, medically appropriate supervision should be maintained. If these patients deteriorate during treatment, appropriate measures should be taken, including discontinuation of therapy.

Serious skin reactions, some of them fatal, including exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis, have been reported very rarely in association with the use of NSAIDs and some selective COX-2 inhibitors during post-marketing surveillance (see UNDESIRABLE EFFECTS). These serious events may occur without warning. Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first month of treatment. Serious hypersensitivity reactions (such as anaphylaxis and angioedema) have been reported in patients receiving etoricoxib (see UNDESIRABLE EFFECTS). Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any drug allergy. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity

ETORICOXIB (ARCOXIA) may mask fever, which is a sign of infection. The physician should be aware of this when using ETORICOXIB (ARCOXIA) in patients being treated for infection.

INTERACTIONS WITH OTHER MEDICAMENTS

Warfarin: In subjects stabilized on chronic warfarin therapy, the administration of ETORICOXIB (ARCOXIA) 120 mg daily was associated with an approximate 13% increase in prothrombin time International Normalized Ratio (INR). Standard monitoring of INR values should be conducted when therapy with ETORICOXIB (ARCOXIA) is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

Rifampin: Co-administration of ETORICOXIB (ARCOXIA) with rifampin, a potent inducer of hepatic metabolism, produced a 65% decrease in etoricoxib plasma area under the curve (AUC). This interaction should be considered when ETORICOXIB (ARCOXIA) is co-administered with rifampin.

Methotrexate: Two studies investigated the effects of ETORICOXIB (ARCOXIA) 60, 90 or 120 mg administered once daily for seven days in patients receiving once-weekly methotrexate doses of 7.5 to 20 mg for rheumatoid arthritis. ETORICOXIB (ARCOXIA) at 60 and 90 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In one study, ETORICOXIB (ARCOXIA) 120 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In the other study, ETORICOXIB (ARCOXIA) 120 mg increased methotrexate plasma concentrations by 28% (as measured by AUC) and reduced renal clearance of methotrexate by 13%. Monitoring for methotrexate-related toxicity should be considered when ETORICOXIB (ARCOXIA) at doses greater than 90 mg daily and methotrexate are administered concomitantly.

Diuretics, Angiotensin Converting Enzyme (ACE) Inhibitors and Angiotensin II Antagonists (AIIAs): Reports suggest that NSAIDs including selective COX-2 inhibitors may diminish the antihypertensive effect of diuretics, ACE inhibitors and AIIAs. This interaction should be given consideration in patients taking ETORICOXIB (ARCOXIA) concomitantly with these products.

In some patients with compromised renal function (e.g., elderly patients or patients who are volume-depleted, including those on diuretic therapy) who are being treated with non-steroidal anti-inflammatory drugs, including selective COX-2 inhibitors, the co-administration of ACE inhibitors or AIIAs may result in a further deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Therefore, the combination should be administered with caution, especially in the elderly.

Lithium: Reports suggest that non-selective NSAIDs and selective COX-2 inhibitors may increase plasma lithium levels. This interaction should be given consideration in patients taking ETORICOXIB (ARCOXIA) concomitantly with lithium.

Aspirin: ETORICOXIB (ARCOXIA) can be used concomitantly with low-dose aspirin at doses for cardiovascular prophylaxis. At steady state, etoricoxib 120 mg once daily had no effect on the anti-platelet activity of low-dose aspirin (81 mg once daily). However, concomitant administration of low-dose aspirin with ETORICOXIB (ARCOXIA) increases rate of GI ulceration or other complications compared to use of ETORICOXIB (ARCOXIA) alone. (See WARNINGS AND PRECAUTIONS.)

Oral Contraceptives: ETORICOXIB (ARCOXIA) 60 mg given concomitantly with an oral contraceptive containing 35 mcg ethinyl estradiol (EE) and 0.5 to 1 mg norethindrone for 21 days increased the steady state $AUC_{0\text{-}24hr}$ of EE by 37%. ETORICOXIB (ARCOXIA) 120 mg given with the same oral contraceptive concomitantly or separated by 12 hours, increased the steady state $AUC_{0\text{-}24hr}$ of EE by 50 to 60%. This increase in EE concentration should be considered when selecting an oral contraceptive for use with etoricoxib. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g., venous thromboembolic events in women at risk.).

Hormone Replacement Therapy: Administration of ETORICOXIB (ARCOXIA) 120 mg with hormone replacement therapy consisting of conjugated estrogens (0.625 mg PREMARIN®) for 28 days, increased the mean steady state $AUC_{0\text{-}24hr}$ of unconjugated estrone (41%), equilin (76%), and 17-β-estradiol (22%). The effect of the recommended chronic doses of ETORICOXIB (ARCOXIA) (30, 60 and 90 mg) has not been studied. The effects of ETORICOXIB (ARCOXIA) 120 mg on the exposure ($AUC_{0\text{-}24hr}$) to these estrogenic components of PREMARIN were less than half of those observed when PREMARIN was administered alone and the dose was increased from 0.625 to 1.25 mg. The clinical significance of these increases is unknown, and higher doses of PREMARIN were not studied in combination with ETORICOXIB (ARCOXIA). These increases in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with ETORICOXIB (ARCOXIA).

Other: In drug-interaction studies, ETORICOXIB (ARCOXIA) did not have clinically important effects on the pharmacokinetics of prednisone/prednisolone or digoxin.

Antacids and ketoconazole (a potent inhibitor of CYP3A4) did not have clinically important effects on the pharmacokinetics of ETORICOXIB (ARCOXIA).

PREGNANCY AND LACTATION

The use of etoricoxib, as with any drug substance known to inhibit COX-2, is not recommended in women attempting to conceive.

No Clinical data on exposed pregnancies are available for etoricoxib. Studies in animals have shown reproductive toxicity. The potential for human risk in pregnancy is unknown. Etoricoxib, as with other medicinal products inhibiting prostaglandin synthesis, may cause uterine inertia and premature closure of

the ductus arteriosus during the last trimester. Etoricoxib is contraindicated in pregnancy. If a woman becomes pregnant during treatment, etoricoxib must be discontinued.

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Reproductive studies conducted in rats have demonstrated no evidence of developmental abnormalities at doses up to 15 mg/kg/day (approximately 1.5 times the human dose [90 mg] based on systemic exposure). At doses approximately 2 times the adult human exposure (90 mg) based on systemic exposure, a low incidence of cardiovascular malformations and increases in post implantation loss were observed in etoricoxib-treated rabbits. No developmental effects were seen at systemic exposure of approximately equal to or less than the daily human dosage (90 mg). However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women.

It is not known whether etoricoxib is excreted in human milk. Etoricoxib is excreted in the milk of lactating rats. Women who use etoricoxib should not breast feed.

PEDIATRIC USE

Safety and effectiveness of etoricoxib in pediatric patients have not been established.

USE IN THE ELDERLY

Pharmacokinetics in the elderly (65 years of age and older) are similar to those in the young. In clinical studies, a higher incidence of adverse experiences was seen in older patients compared to younger patients; the relative differences between etoricoxib and control groups were similar in the elderly and the young. Greater sensitivity of some older individuals cannot be ruled out.

UNDESIRABLE EFFECTS

In clinical trials, ETORICOXIB (ARCOXIA) was evaluated for safety in 7152 individuals, including 4488 patients with OA, RA or chronic low back pain (approximately 600 patients with OA or RA were treated for one year or longer).

The following drug-related adverse experiences were reported in clinical studies in patients with OA, RA, or chronic low back pain treated for up to 12 weeks. These occurred in ≥1% of patients treated with ETORICOXIB (ARCOXIA) and at an incidence greater than placebo: asthenia/fatigue, dizziness, lower extremity edema, hypertension, dyspepsia, heartburn, nausea, headache, ALT increased, AST increased.

The adverse experience profile was similar in patients with OA or RA treated with ETORICOXIB (ARCOXIA) for one year or longer.

In the MEDAL Study, an endpoint driven CV outcomes trial involving 23, 504 patients, the safety of ETORICOXIB (ARCOXIA) 60 or 90 mg daily was compared to diclofenac 150 mg daily in patients with OA or RA (mean duration of treatment was 20 months). In this large trial, only serious adverse events and discontinuations due to any adverse events were recorded. The rates of confirmed thrombotic cardiovascular serious adverse events were similar between ETORICOXIB (ARCOXIA) and diclofenac. The incidence of discontinuations for hypertension-related adverse events was less than 3% in each treatment group; however, ETORICOXIB (ARCOXIA) 60 and 90 mg demonstrated significantly higher rates of discontinuations for these events than diclofenac. The incidence of congestive heart failure adverse events (discontinuations and serious events) and the incidence of discontinuations due to edema occurred at similar rates on ETORICOXIB (ARCOXIA) 60 mg compared to diclofenac; however, the incidences for these events were higher for ETORICOXIB (ARCOXIA) 90 mg compared to diclofenac. The incidence of discontinuations due to atrial fibrillation was higher for etoricoxib compared to diclofenac.

The EDGE and EDGE II studies compared the GI tolerability of etoricoxib 90 mg daily (1.5 to 3 times the doses recommended for OA) and diclofenac 150 mg daily in 7111 patients with OA (EDGE Study; mean duration of treatment 9 months) and 4086 patients with RA (EDGE II; mean duration of treatment 19 months). In each of these studies, the adverse experience profile on ETORICOXIB (ARCOXIA) was generally similar to that reported in the phase IIb/III placebo-controlled clinical studies; however, hypertension and edema-
related adverse experiences occurred at a higher rate on etoricoxib 90 mg than on diclofenac 150 mg daily. The rate of confirmed thrombotic cardiovascular serious adverse events occurring in the two treatment groups was similar.

In a combined analysis of phase IIb to V clinical studies of 4 weeks duration or longer (excluding the MEDAL Program Studies), there was no discernible difference in the rate of confirmed thrombotic cardiovascular serious adverse events between patients receiving etoricoxib ≥30 mg or non-naproxen NSAIDs. The rate of these events was higher in patients receiving etoricoxib compared with those receiving naproxen 500 mg twice daily.

In a clinical study for ankylosing spondylitis, patients were treated with ETORICOXIB (ARCOXIA) 90 mg once daily for up to 1 year (N=126). The adverse experience profile in this study was generally similar to that reported in chronic studies in OA, RA and chronic low back pain.

In a clinical study for acute gouty arthritis, patients were treated with ETORICOXIB (ARCOXIA) 120 mg once daily for eight days. The adverse experience profile in this study was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

In clinical studies for acute analgesia, patients were treated with ETORICOXIB (ARCOXIA) 120 mg once daily for one to seven days. The adverse experience profile in these studies was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

Post-marketing experience

The following adverse reactions have been reported in post-marketing experience:
Blood and lymphatic system disorders: thrombocytopenia.
Immune system disorders: hypersensitivity reactions, including anaphylactic/anaphylactoid reactions including shock.
Metabolism and nutrition disorders: hyperkalemia.
Psychiatric disorders: anxiety, insomnia, confusion, hallucinations, depression, restlessness.
Nervous system disorders: dysgeusia, somnolence.
Eye disorders: blurred vision.
Cardiac disorders: congestive heart failure, palpitations, angina, arrhythmia.
Vascular disorders: hypertensive crisis.
Respiratory, thoracic and mediastinal disorders: bronchospasm.
Gastrointestinal disorders: abdominal pain, oral ulcers, peptic ulcers including perforation and bleeding (mainly in elderly patients), vomiting, diarrhea.
Hepatobiliary disorders: hepatitis, jaundice.
Skin and subcutaneous tissue disorders: angioedema, pruritus, erythema, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria.
Renal and urinary disorders: renal insufficiency, including renal failure (see WARNINGS AND PRECAUTIONS).

OVERDOSE AND TREATMENT

In clinical studies, administration of ETORICOXIB (ARCOXIA) at single doses up to 500 mg and multiple doses up to 150 mg/day for 21 days did not result in significant toxicity. There have been reports of acute

overdosage with etoricoxib, although adverse experiences were not reported in the majority of cases. The most frequently observed adverse experiences were consistent with the safety profile for etoricoxib (e.g. gastrointestinal events, renovascular events).

In the event of overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring, and institute supportive therapy, if required.

Etoricoxib is not dialyzable by hemodialysis; it is not known whether etoricoxib is dialyzable by peritoneal dialysis.

STORAGE CONDITION

Store below 30°C. Protect from light. Store in the original package.

DOSAGE FORMS AND PACKAGING AVAILABLE

Each tablet of ETORICOXIB (ARCOXIA / ARCOXIA Ac) for oral administration contains either 30, 60, 90 or 120 mg of etoricoxib.

ETORICOXIB (ARCOXIA) 30mg is available in alu/alu blister pack of 10's (box of 30's).

ETORICOXIB (ARCOXIA / ARCOXIA Ac) 60mg, 90mg and 120mg are available in alu/alu blister pack x 5's (box of 30's).

CAUTION

Foods, Drugs, Devices and Cosmetics Act prohibits dispensing without the prescription of a physician.

DATE OF REVISION OF PACKAGE INSERT

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MSD

Manufactured by
MERCK SHARP & DOHME CORP.
2778 South East Side Highway,
Elkton, VA 22827, U.S.A.

Packed by
MERCK SHARP & DOHME (Australia) Pty. Ltd.
54-68 Ferndell Street,
South Granville, N.S.W., 2142 AUSTRALIA

Imported by
MERCK SHARP & DOHME (I.A.) CORP.
26/F Philamlife Tower, 8767 Paseo de Roxas
Makati City, Philippines