Tablets
ARCOXIA®
(etoricoxib, MSD)

THERAPEUTIC CLASS

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

CLINICAL PHARMACOLOGY

Mechanism of Action

ARCOXIA is a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic, and antipyretic activities in animal models. ARCOXIA is a potent, orally active, highly selective cyclooxygenase-2 (COX-2) inhibitor within and above the clinical dose range. Two isoforms of cyclooxygenase have been identified: cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). COX-1 is responsible for prostaglandin-mediated normal physiologic functions such as gastric cytoprotection and platelet aggregation. Inhibition of COX-1 by nonselective NSAIDs has been associated with gastric damage and platelet inhibition. COX-2 has been shown to be primarily responsible for the synthesis of prostanoid mediators of pain, inflammation, and fever. Selective inhibition of COX-2 by etoricoxib decreases these clinical signs and symptoms with decreased GI toxicity and without effects on platelet function.

Across clinical pharmacology studies, ARCOXIA produced dose-dependent inhibition of COX-2 without inhibition of COX-1 at doses up to 150 mg daily.

The influence on gastroprotective COX-1 activity was also assessed in a clinical study where prostaglandin synthesis was measured in gastric biopsy samples from subjects administered either ARCOXIA 120 mg daily, naproxen 500 mg twice daily, or placebo. ARCOXIA did not inhibit gastric prostaglandin synthesis as compared to placebo. In contrast, naproxen inhibited gastric prostaglandin synthesis by approximately 80% compared with placebo. These data further support the COX-2 selectivity of ARCOXIA.

Platelet Function

Multiple doses of ARCOXIA up to 150 mg administered daily up to nine days had no effect on bleeding time relative to placebo. Similarly, bleeding time was not altered in a single dose study with ARCOXIA 250 or 500 mg. There was no inhibition of *ex vivo* arachidonic acid- or collagen-induced platelet aggregation at steady state with doses of ARCOXIA up to 150 mg. These findings are consistent with the COX-2 selectivity of etoricoxib.

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.

The onset of analgesia with ARCOXIA occurred as early as 24 minutes after dosing and persisted for as long as 24 hours.

A standard meal had no clinically meaningful effect on the extent or rate of absorption of a dose of etoricoxib 120 mg. A high-fat meal had no effect on the extent of absorption of etoricoxib, although it did decrease the rate of absorption (reduced C_{max} for 36% and delayed T_{max} for 2 hours). 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 DOSAGE AND ADMINISTRATION.)

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 DOSAGE AND ADMINISTRATION.)

Race

There is no clinically important effect of race on the pharmacokinetics of etoricoxib. (See DOSAGE AND ADMINISTRATION.)

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. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). (See DOSAGE AND ADMINISTRATION, *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

ARCOXIA is indicated for:

- Acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA)
- Treatment of acute gouty arthritis
- 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 PRECAUTIONS).

DOSAGE AND ADMINISTRATION

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

Arthritis

Osteoarthritis

The recommended dose is 60 mg once daily.

Rheumatoid Arthritis

The recommended dose is 90 mg once daily.

Acute Gouty Arthritis

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

Analgesia

Primary Dysmenorrhea

The recommended dose is 120 mg once daily. 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 each indication is the maximum recommended dose.

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 PRECAUTIONS)

Elderly, Gender, Race

No dosage adjustment in 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. There are no clinical or pharmacokinetic data in patients with severe hepatic insufficiency (Child-Pugh score >9). (See PRECAUTIONS.)

Renal Insufficiency

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

CONTRAINDICATIONS

ARCOXIA is contraindicated in patients with:

Hypersensitivity to any component of this product.

Congestive heart failure (NYHA II-IV).

Established ischemic heart disease, peripheral arterial disease and/or cerebrovascular disease (including patients who have recently undergone coronary artery bypass graft surgery or angioplasty).

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, hyperlipidaemia, 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.

In patients with advanced renal disease, treatment with ARCOXIA is not recommended. Clinical experience in patients with estimated creatinine clearance of <30 mL/min is very limited. If therapy with ARCOXIA must be initiated in such patients, close monitoring of the patient's renal function is advisable.

Renal prostaglandins may play a compensatory role in the maintenance of renal perfusion. Therefore, under conditions of compromised renal perfusion, administration of 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. As with other drugs known to inhibit prostaglandin synthesis, discontinuation of therapy with ARCOXIA would be expected to be followed by recovery to the pretreatment state.

Caution should be used when initiating treatment with ARCOXIA in patients with considerable dehydration. It is advisable to rehydrate patients prior to starting therapy with ARCOXIA.

As with other drugs known to inhibit prostaglandin synthesis, fluid retention, edema and hypertension have been observed in some patients taking ARCOXIA. The possibility of fluid retention, edema or hypertension should be taken into consideration when ARCOXIA is used in patients with pre-existing edema, hypertension, or heart failure. 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.

Warnings:

Serious cardiovascular side effects have been reported by patients taking drugs in the same class and long-term safety of people taking the medicine have not been established. Precautions for administration should be taken for patients with history of cardiovascular diseases.

1. Caution should be exercised in patients with a medical history of ischemic heart disease.

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.

2. Independent of treatment with ARCOXIA, 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.

Physician should be aware that patients may develop upper gastrointestinal (GI) ulcers/ulcer complications irrespective of treatment. In clinical studies the risk of endoscopically detected upper GI ulcers was lower in patients treated with 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 ARCOXIA 120 mg it was higher than in patients treated with placebo. Upper GI ulcers/ulcer complications have occurred in patients treated with ARCOXIA.

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 ARCOXIA 60 and 90 mg daily. In active comparator portions of clinical trials, the incidence of elevated AST and/or ALT in patients treated with ARCOXIA 60 and 90 mg daily was similar to that of patients treated with naproxen, but notably less than the incidence in the diclofenac group. These elevations resolved in patients treated with ARCOXIA, with approximately half resolving while patients remained on therapy.

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, ARCOXIA should be discontinued.

ARCOXIA should be used with caution in patients who have previously experienced acute asthmatic attacks, urticaria, or rhinitis, which were precipitated by salicylates or non-selective cyclooxygenase inhibitors. Since the pathophysiology of these reactions is unknown, physicians should weigh the potential benefits of prescribing ARCOXIA versus the potential risks.

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 SIDE EFFECTS). 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 SIDE 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.

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

PREGNANCY

As with other drugs known to inhibit prostaglandin synthesis, use of ARCOXIA should be avoided in late pregnancy because it may cause premature closure of the ductus arteriosus.

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 (90mg). However, animal reproduction studies are not always predictive of human response. There are no adequate and well-controlled studies in pregnant women. ARCOXIA should be used during the first two trimesters of pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

Etoricoxib is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the possible adverse effects of drugs that inhibit prostaglandin synthesis on nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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, no overall differences in safety or effectiveness were observed between elderly and younger patients.

DRUG INTERACTIONS

***Warfarin*:** In subjects stabilized on chronic warfarin therapy, the administration of 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 ARCOXIA is initiated or changed, particularly in the first few days, in patients receiving warfarin or similar agents.

***Rifampin*:** Co-administration of 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 ARCOXIA is co-administered with rifampin.

***Methotrexate*:** Two studies investigated the effects of 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. ARCOXIA at 60 and 90 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In one study, ARCOXIA 120 mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In the other study, 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 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 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 ARCOXIA concomitantly with lithium.

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

***Oral Contraceptives*:** 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%. ARCOXIA 120 mg given with the same oral contraceptive, either 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 appropriate oral contraceptive for use with ARCOXIA. An increase in EE exposure can increase the incidence of adverse events associated with oral contraceptives (e.g., venous thrombo-embolic events in women at risk).

***Hormone Replacement Therapy*:** Administration of ARCOXIA 120 mg with hormone replacement therapy consisting of conjugated estrogens (0.625 mg PREMARINTM<or local TRADEMARK>) for 28 days, increased the mean steady state AUC0-24hr of unconjugated estrone (41%), equilin (76%), and 17-β-estradiol (22%). The effect of the recommended chronic doses of ARCOXIA (60 and 90 mg) has not been studied. The effects of ARCOXIA 120 mg on the exposure (AUC0-24hr) to these estrogenic components of PREMARIN <or local TRADEMARK> were less than half of those observed when PREMARIN <or local TRADEMARK> 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 <or local TRADEMARK> were not studied in combination with ARCOXIA. These increases in estrogenic concentration should be taken into consideration when selecting post-menopausal hormone therapy for use with ARCOXIA.

***Other**:* In drug-interaction studies, 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 ARCOXIA.

SIDE EFFECTS

In clinical trials, ARCOXIA was evaluated for safety in approximately 4800 individuals, including approximately 3400 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 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 ARCOXIA for one year or longer.

Seven thousand one hundred eleven patients were enrolled in an additional study in OA that compared the GI tolerability of etoricoxib 90 mg once daily (1.5 times above the dose recommended for OA) and diclofenac sodium 50 mg 3 times daily over a mean period of 9 months. The adverse experience profile on ARCOXIA was generally similar to that reported in the Phase IIb/III placebo-controlled clinical studies; however, hypertension adverse experiences occurred at a higher rate on ARCOXIA than on diclofenac. The rate of serious thrombotic cardiovascular events occurring in the two treatment groups was similar.

In the initial clinical development program, approximately 3100 patients were treated with etoricoxib ≥60 mg daily for 12 weeks or longer. There was no discernible difference in the rate of serious thrombotic cardiovascular events between patients receiving etoricoxib ≥60 mg or non-naproxen NSAIDs. However, 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 acute gouty arthritis, patients were treated with 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 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:

Immune system disorders: hypersensitivity reactions, including anaphylactic/ anaphylactoid reactions.

Psychiatric disorders: anxiety, insomnia, confusion, hallucinations.

Nervous system disorders: dysgeusia, somnolence.

Cardiac disorders: congestive heart failure.

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.

Skin and subcutaneous tissue disorders: angioedema, pruritus, rash, Stevens-Johnson syndrome, urticaria

Renal and urinary disorders: renal insufficiency, including renal failure, usually reversible upon discontinuation of therapy (see PRECAUTIONS).

OVERDOSAGE

No overdoses of ARCOXIA were reported during clinical trials.

In clinical studies, administration of 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.

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

Blisters: Store below 30°C (86°F). Store in the original package.

AVAILABILITY

To be filled in locally.

Manufactured by Merck & Co., Inc., 2778 S. East Side Highway, Elkton, Virginia 22827, USA.