LPC-OG0663-T-012023-Malaysia

LOCAL PRODUCT CIRCULAR

Tablets
ARCOXIA®

(etoricoxib)

I. 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).

II. COMPOSITION

IIa. Active Ingredients

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

IIb. Inactive Ingredients

Each tablet contains calcium hydrogen phosphate (anhydrous), carnauba wax, croscarmellose sodium, hypromellose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, titanium dioxide, and glycerol triacetate. The 30 mg, 60 mg and 120 mg tablets also contain yellow ferric oxide and FD&C Blue #2 (indigo carmine lake).

III. INDICATIONS

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
- Chronic low back pain (30 mg and 60 mg only)
- Treatment of acute pain, including that related to primary dysmenorrhoea and minor dental procedures.

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

IV. DOSAGE AND ADMINISTRATION

ARCOXIA is administered orally. ARCOXIA may be taken with or without food. ARCOXIA shouldbe administered for the shortest duration possible and the lowest effective daily dose should be used.

Osteoarthritis

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

Rheumatoid Arthritis

The recommended dose is 60 mg or 90 mg once daily. The minimum effective daily dose is 60 mg once daily. In some patients, 90 mg once daily may provide increased therapeutic benefit.

Ankylosing Spondylitis

The recommended dose is 60 mg or 90 mg once daily. The minimum effective daily dose is60 mg once daily. In some patients, 90 mg once daily may provide increased therapeutic benefit.

Chronic low back pain

The recommended dose is 60 mg once daily

Acute Pain

In the following acute painful conditions, ARCOXIA should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment:

Acute Gouty Arthritis

The recommended dose is 120 mg once daily.

Primary Dysmenorrhea

The recommended dose is 120 mg once daily.

Minor Dental Procedures

The recommended dose is 90 mg once daily.

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.
The dose of chronic low back pain should not exceed 60 mg daily.
The dose for minor dental procedures should not exceed 90 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 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, 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 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).

V. CLINICAL PHARMACOLOGY

IIIa. 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.

IIIb. Pharmacokinetics

IIIb-1. Absorption

In studies specifically designated to measure the onset of action of etoricoxib, the onset of action occurred as early as 24 minutes after dosing.

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 theclinical 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/aluminium hydroxide antacid, or a calcium carbonate antacid (approximately 50 mEq acid-neutralizing capacity).

IIIb-2. 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.

IIIb-3. 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.

IIIb-4. 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.

VI. 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).

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

Pregnancy.

VII. 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.

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

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 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. All Nonsteroidal Antiinflammatory Drugs (NSAIDs), including etoricoxib, can be associated with new onset or recurrent congestive heart failure. (See SIDE 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 ARCOXIA, the results of the MEDAL Program demonstrate that in patients treated with ARCOXIA, the risk of GI toxicity with 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 ARCOXIA 120 mg once daily than in patients treated with the 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. 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 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 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 ARCOXIA, with approximately half resolving while patients remained on therapy. In controlled clinical trials of 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, 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). 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 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.

VIII. WARNINGS

RISK OF GI ULCERATION, BLEEDING AND PERFORATION WITH NSAIDs

Serious GI toxicity such as bleeding, ulceration and perforation can occur at any time, with or without warning symptoms, in patients treated with NSAIDs therapy. Although minor upper GI problems (e.g. dyspepsia) are common, usually developing early in therapy, prescribers should remain alert for ulceration and bleeding in patients treated with NSAIDs even in the absence of previous GI tract symptoms.

Studies to date have not identified any subset of patients not at risk of developing peptic ulceration and bleeding. Patients with prior history of serious adverse events and other risk factors associated with peptic ulcer disease (e.g. alcoholism, smoking and corticosteroid therapy) are at increased risk. Elderly or debilitated patients seem to tolerate ulceration or bleeding less than other individuals and account for most spontaneous reports for fatal GI events.

IX. PREGNANCY

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. Cases of fetal renal dysfunction that have resulted in reduction of amniotic fluid volume (oligohydramnios) have been reported in pregnant women treated with non-steroidal anti-inflammatory drugs (NSAIDs) at 20 weeks of gestation or later. In some cases, this may result in neonatal renal dysfunction. Such effects may occur shortly after NSAID treatment initiation; oligohydramnios is often reversible after treatment discontinuation. Etoricoxib is contraindicated in pregnancy. If a woman becomes pregnant during treatment, etoricoxib should be discontinued.

X. 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.

XI. PEDIATRIC USE

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

XII. 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.

XIII. 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. 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 ARCOXIA increases the rate of GI ulceration or other complications compared to use of ARCOXIA alone. (see PRECAUTIONS).

Oral Contraceptives: ARCOXIA 60mg 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 PREMARIN®) for 28 days, increased the mean steady state $AUC_{0\text{-}24hr}$ of unconjugated estrone (41%), equilin (76%) and 17-ß-estradiol (22%). The effect of the recommended chronic doses of ARCOXIA (30, 60 and 90 mg) has not been studied. The effects of ARCOXIA 120mg 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 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.

XIV. SIDE EFFECTS

In clinical trials, ARCOXIA was evaluated for safety in 9295 individuals, including 5774 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.

In the MEDAL Study, an endpoint driven CV outcomes trial involving 23, 504 patients, the safety of 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 ARCOXIA and diclofenac. The incidence of discontinuations for hypertension-related adverse events was less than 3% in each treatment group; however, 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 ARCOXIA 60 mg compared to diclofenac, however, the incidences for these events were higher for 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 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 ARCOXIA 90 mg once daily for up to 1 year (N=126). In another clinical study for ankylosing spondylitis (N=857), patients were treated with ARCOXIA 60 mg or 90 mg once daily for up to 26 weeks. The adverse experience profile in these studies 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 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 initial 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.

In the combined studies for acute post-operative dental pain, the incidence of post-dental extraction alveolitis (dry socket) reported in patients treated with ARCOXIA was similar to that of patients treated with active comparators.

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, anaphylactic/anaphylactoid reactions including shock.

Metabolism and nutrition disorders: hyperkalemia.

Psychiatric disorders: anxiety, insomnia, confusion, hallucinations, depression, restlessness.

Nervous system disorders: dysgeusia, somnolence, intracranial hemorrhage.

Eye disorders: blurred vision.

Cardiac disorders: congestive heart failure, palpitations, angina, arrhythmia.

Vascular disorders: hypertensive crisis, deep vein thrombosis.

Respiratory, thoracic and mediastinal disorders: bronchospasm, pulmonary embolism.

Gastrointestinal disorders: abdominal pain, oral ulcers, peptic ulcers including perforation and bleeding (mainly in elderly patients), vomiting, diarrhea.

Hepatobiliary disorders: hepatitis, jaundice, hepatic failure.

Skin and subcutaneous tissue disorders: angioedema, pruritus, erythema, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, fixed drug eruption.

Renal and urinary disorders: renal insufficiency, including renal failure (see PRECAUTIONS).

XV. OVERDOSAGE

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. 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 experience 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.

XVI. AVAILABILITY

ARCOXIA 30mg: Available in blister packs of 10's, 30's & 100's per pack
ARCOXIA 60mg: Available in blister packs of 10's & 100's per pack
ARCOXIA 90mg: Available in blister packs of 10's, 30's & 100's per pack
ARCOXIA 120mg: Available in blister packs of 30's per pack

Not all pack sizes may be marketed

XVII. PHYSICAL APPEARANCE

ARCOXIA 30mg: Blue-green apple-shape biconvex film coated tablets debossed ACX 30 on one side and 101 on the other side

ARCOXIA 60mg: Dark green apple-shape biconvex film coated tablets debossed ARCOXIA 60 on one side and 200 on the other side

ARCOXIA 90mg: White apple-shape biconvex film coated tablets debossed ARCOXIA 90 on one side and 202 on the other side

ARCOXIA 120mg: Pale green apple-shape biconvex film coated tablets debossed ARCOXIA 120 on one side and 204 on the other side

XVIII. STORAGE

Store at 30 ° C (86 ° F). Store in the original package. Protect from moisture and light.

XIX. SHELF LIFE

Please refer to the expiry date on the outer carton.

XX. MANUFACTURER

Rovi Pharma Industrial Services,
S.A.Vía Complutense, 140
28805 Alcalá de
HenaresMadrid,
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XXI. PRODUCT REGISTRATION HOLDER

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