

NEW ZEALAND DATA SHEET

1 ARCOXIA® (etoricoxib) film coated tablets

ARCOXIA® 30mg film coated tablets

ARCOXIA® 60mg film coated tablets

ARCOXIA® 90mg film coated tablets

ARCOXIA® 120mg film coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 30, 60, 90 or 120 mg of etoricoxib.

Excipients with known effect:

30 mg tablet: 1.4 mg lactose (as monohydrate)

60 mg tablet: 2.8 mg lactose (as monohydrate)

90 mg tablet: 4.2 mg lactose (as monohydrate)

120 mg tablet: 5.6 mg lactose (as monohydrate)

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

30mg tablet: A blue green apple shaped biconvex film coated tablet debossed 101 on one side and ACX 30 on the other. Dimensions are 5.69 mm x 5.54 mm.

60mg tablet: A dark green apple shaped biconvex film coated tablet debossed 200 on one side and ARCOXIA 60 on the other. Dimensions are 7.16 mm x 6.99 mm.

90mg tablet: A white apple shaped biconvex film coated tablet debossed 202 on one side and ARCOXIA 90 on the other. Dimensions are 8.20 mm x 8.00 mm.

120mg tablet: A pale green apple shaped biconvex film coated tablet debossed 204 on one side and ARCOXIA 120 on the other. Dimensions are 9.03 mm x 8.80 mm.

Do not halve tablet. Studies on divided tablets have not been performed.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

ARCOXIA is indicated for:

- Acute and chronic treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA)
- The management of ankylosing spondylitis (AS)
- Treatment of acute gouty arthritis
- Relief of acute pain, including pain related to minor dental procedures
- Relief of chronic musculoskeletal pain

The decision to prescribe a selective COX-2 inhibitor should only be made:

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- if non-pharmacological interventions and simple analgesic therapy i.e paracetamol have been tried and found to lack analgesic efficacy or to have unacceptable adverse effects in the individual patient; and
- after assessment of the individual patient's overall risk factors for developing severe adverse events e.g. history of cardiovascular, renal, or gastrointestinal disease (see section 4.3 and 4.4).

4.2 Dose and method of administration

ARCOXIA is administered orally. ARCOXIA may be taken with or without food. Do not halve tablets. Studies on divided tablets have not been performed.

Arthritis

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. However, dose escalation from 60 mg to 90 mg should be considered on individual patient basis.

Ankylosing Spondylitis: 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. However, dose escalation from 60 mg to 90 mg should be considered on individual patient basis.

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

Acute Pain: 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.

Dental Pain: The recommended dose is 90 mg once daily. ARCOXIA 90 mg should be used only for the acute symptomatic period, limited to a maximum of 8 days treatment.

Chronic Musculoskeletal Pain: The recommended dose is 60 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 should not exceed 120 mg daily.

The dose for dental pain should not exceed 90 mg daily.

The dose for chronic pain should not exceed 60 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. Patients on long-term treatment should be reviewed regularly, such as

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every three months, with regards to efficacy, risk factors and ongoing need for treatment (see section 4.1 and 4.4).

Special Populations

Paediatric Population

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

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 section 4.4).

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 section 4.4).

4.3 Contraindications

ARCOXIA is contraindicated in patients with:

- hypersensitivity to any component of this product.
- a history of asthma, urticarial or other allergic reactions after taking aspirin or other NSAIDs.
- congestive heart failure (NYHA II-IV).
- hypertension whose blood pressure is persistently above 140/90 mmHg and has not been adequately controlled.
- established ischaemic heart disease, peripheral artery disease and/or cerebrovascular disease (including patients who have recently undergone coronary artery bypass graft surgery or angioplasty).
- use in the peri-operative period in patients undergoing cardiac or major vascular surgery.
- severe hepatic dysfunction (serum albumin <25 g/L or Child-Pugh score ≥10).
- active peptic ulceration or gastrointestinal bleeding.
- an estimated creatinine clearance < 30mL/min.

4.4 Special warnings and precautions for use

Cardiovascular Effects

Clinical trials suggest that the selective COX-2 inhibitor class of medicines (of which etoricoxib is one) may be associated with an increased risk of thrombotic events (especially MI and stroke), relative to placebo and some Non-steroidal Anti-inflammatory Drugs, 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. Patients on long-term treatment should be reviewed regularly,

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such as every three months, with regards to efficacy, risk factors and ongoing need for treatment.

Prescribers should inform the individual patient of the increased risk when prescribing etoricoxib to patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking).

Two large, controlled clinical trials of a different COX-2 selective inhibitor for the treatment of pain in the first 10-14 days following CABG surgery found an increased incidence of myocardial infarction and stroke. In the absence of comparable data with etoricoxib, it may be assumed that patients at high risk of cardiovascular disease (including patients with diabetes, hyperlipidaemia, hypertension, or smokers) who are undergoing any major surgery may face an increased risk of developing a cardiovascular event. Patients with significant risk factors for cardiovascular events should only be treated with etoricoxib after careful consideration of the patient's overall risk and the potential risks and benefits of alternative analgesic therapies.

Aspirin Substitution

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 no evidence that concurrent use of aspirin decreases the risk of cardiovascular adverse events associated with COX-2 inhibitors, including etoricoxib.

Gastrointestinal Effects

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 120mg 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.

Patients should be informed about the signs and/or symptoms of serious GI toxicity and the steps to take if they occur. The utility of periodic laboratory monitoring has not been demonstrated, nor has it been adequately assessed. Only one in five patients who develop a serious upper GI adverse event on NSAID therapy is symptomatic. It has been demonstrated that upper GI ulcers, gross bleeding or perforation, caused by NSAIDs, appear to occur in approximately 1% of patients treated for 3-6 months, and in about 2-4% of patients treated for one year. These trends continue, thus increasing the likelihood of developing a serious GI event at some time during the course of therapy. However, even short-term therapy is not without risk.

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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.

Renal Effects

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.

Fluid Retention, Oedema, Hypertension

As with other medicines known to inhibit prostaglandin synthesis, fluid retention, oedema and hypertension have been observed in some patients taking ARCOXIA. The possibility of exacerbating fluid retention, oedema or hypertension should be taken into consideration when ARCOXIA is used in patients with pre-existing oedema, hypertension, or heart failure. Close monitoring is essential. All NSAIDs, including etoricoxib, can be associated with new onset or recurrent congestive heart failure (see section 4.8).

Etoricoxib may be associated with more frequent and severe hypertension than some other NSAIDs and selective COX-2 inhibitors, particularly at high doses. Therefore, hypertension should be controlled before treatment with etoricoxib (see Contraindications) and special attention should be paid to blood pressure monitoring during treatment with etoricoxib. Blood pressure should be monitored within two weeks after initiation of treatment and periodically thereafter. If blood pressure rises significantly, alternative treatment should be considered.

Hepatic Effects

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 150mg 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.

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In post-marketing experience, jaundice has been reported rarely. Limited reports of hepatic failure have been reported, but without clear association to ARCOXIA. 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.

Hypersensitivity

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.

General

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

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 section 4.8). 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 section 4.8). Some selective COX-2 inhibitors have been associated with an increased risk of skin reactions in patients with a history of any medicine allergy. Etoricoxib should be discontinued at the first appearance of skin rash, mucosal lesions, or any other sign of hypersensitivity.

Use in Patients with Fever and Infection

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.

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. As with any NSAID, caution should be exercised in treating the elderly (65 years and older).

4.5 Interaction with other medicines and other forms of interaction

Warfarin: In subjects stabilised on chronic warfarin therapy, the administration of ARCOXIA 120 mg daily was associated with an approximate 13% increase in prothrombin time International Normalised Ratio (INR). Standard monitoring of INR values should be

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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 20mg for rheumatoid arthritis. ARCOXIA at 60 and 90mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In one study, ARCOXIA 120mg had no effect on methotrexate plasma concentrations (as measured by AUC) or renal clearance. In the other study, ARCOXIA 120mg 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 90mg 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 medicines, 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: There is no evidence that concurrent use of aspirin decreases the risk of cardiovascular adverse events associated with COX-2 inhibitors, including etoricoxib. However concomitant administration of low-dose aspirin with ARCOXIA results in an increased rate of GI ulceration or other complications compared to use of ARCOXIA alone. At steady state, etoricoxib 120mg once daily had no effect on the anti-platelet activity of low-dose aspirin (81mg once daily) (see section 4.4).

Oral Contraceptives: ARCOXIA 60mg given concomitantly with an oral contraceptive containing 35mcg ethinyl estradiol (EE) and 0.5 to 1mg norethindrone for 21 days increased the steady state $AUC_{0-24 \text{ hr}}$ of EE by 37%. ARCOXIA 120mg given with the same oral contraceptive, either concomitantly or separated by 12 hours, increased the steady state $AUC_{0-24 \text{ hr}}$ 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).

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

Other: In medicine-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.

4.6 Fertility, pregnancy and lactation

Pregnancy

Category C *Medicines which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human foetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details.*

As with other medicines 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 (90 mg). 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 foetus.

Data from epidemiological studies suggest an increased risk of miscarriage after the use of a prostaglandin synthesis inhibitor in early pregnancy.

Breastfeeding

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

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Fertility

For fertility information from animal studies, see section 5.3, Reproduction.

4.7 Effects on ability to drive and use machines

There is no information to suggest that ARCOXIA affects a patient's ability to drive or operate machinery. However, based on its pharmacodynamic properties and overall safety profile, it is presumed to be safe or unlikely to produce an effect on the ability to drive or use machinery.

4.8 Undesirable effects

Osteoarthritis, Rheumatoid Arthritis and Chronic Pain

5774 patients with OA, RA, or chronic low back pain were treated with ARCOXIA; approximately 1,200 patients received ARCOXIA for six months or longer and approximately 600 patients for one year or longer. The following table lists all adverse events, regardless of causality, occurring in at least 2% of patients receiving ARCOXIA 60 or 90 mg daily in six placebo-controlled studies of 12-weeks duration conducted in patients with OA, RA, or chronic low back pain.

Table 1 Clinical Adverse Experiences occurring in $\geq 2.0\%$ of Patients Treated with ARCOXIA

	Placebo (N = 1011)	ARCOXIA 60 or 90mg daily (N = 1547)	Naproxen 1000mg daily (N = 790)
Body as a Whole/ Site Unspecified			
Asthenia/Fatigue	1.3	2.2	1.8
Dizziness	1.3	2.1	2.5
Lower Extremity Oedema	1.9	2.1	2.3
Upper Respiratory Infection	4.0	5.4	6.3
Cardiovascular System			
Hypertension	1.5	3.6	2.8
Digestive System			
Diarrhoea	4.0	4.6	2.8
Epigastric Discomfort	1.7	2.0	3.8
Heartburn	1.3	2.2	4.2
Nausea	2.6	3.5	4.1
Eyes, Ears, Nose, and Throat			
Sinusitis	2.1	2.0	1.3
Nervous System			
Headache	4.8	5.9	3.2
Urogenital System			
Urinary Tract Infection	3.4	2.9	3.0

The following adverse events occurred in patients treated with ARCOXIA 30, 60 or 90 mg daily at an incidence $>0.1\%$ to 1.9% and at least 0.1% greater than placebo (regardless of

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causality) in eleven placebo-controlled studies of 12 weeks duration in patients with OA, RA or chronic low back pain:

Infections and infestations: bacterial infection, bronchitis, cystitis, folliculitis, fungal infection, gastroenteritis, herpes simplex, herpes zoster, laryngitis, onychomycosis, pharyngitis, pneumonia, skin infection, tinea pedis, vaginal infection.

Neoplasms benign, malignant and unspecified (including cysts and polyps): basal cell carcinoma, breast malignant neoplasm.

Blood and lymphatic system disorders: anaemia.

Immune system disorders: allergy, medicine allergy.

Metabolism and nutrition disorders: anorexia, appetite change, diabetes mellitus, hyperglycaemia.

Psychiatric disorders: anxiety, depression, dream abnormality, insomnia.

Nervous system disorders: dysgeusia, hypoesthesia, hyporeflexia, lumbar radiculopathy, median nerve neuropathy, memory impairment, mental acuity decreased, paresthaesia, sciatica, transient ischaemic attack, tremor.

Eye disorders: cataract, conjunctivitis, Sicca syndrome, visual disturbance.

Ear and labyrinth disorders: otic pain, tinnitus.

Cardiac disorders: angina pectoris, atrial flutter, congestive heart failure, palpitation.

Vascular disorders: flushing, diastolic hypertension, orthostatic hypotension.

Respiratory, thoracic and mediastinal disorders: cough, dyspnoea, epistaxis, sinus congestion, rales.

Gastrointestinal disorders: acid reflux, abdominal distension, aphthous stomatitis, bloating feeling, bowel movement pattern change, constipation, dental pain, digestive gas symptoms, dry mouth, dyspepsia, flatulence, gastritis, gastrointestinal disorder, gastrointestinal distress, gingival disorder, haemorrhoids, irritable bowel syndrome, oral lesion, oral ulcer, tongue oedema, vomiting.

Hepatobiliary disorders: fatty liver.

Skin and subcutaneous tissue disorders: alopecia, cutaneous nodule, dermatitis, ecchymosis, eczema, exanthema, non-specific skin disorder, pruritus, rosacea, skin ulcer.

Musculoskeletal and connective tissue disorders: ankle pain, arthralgia, bursitis, costochondritis, finger pain, foot pain, hip pain, muscular cramp, muscular weakness, neck pain, peri-arthritis, shoulder pain, tendonitis, tenosynovitis.

Renal and urinary disorders: erythrocyturia, glycosuria, haematuria, nocturia, proteinuria.

Reproductive system and breast disorders: ovarian cyst, vaginal haemorrhage.

General disorders and administration site conditions: body ache, chest pain, oedema, facial oedema, peripheral oedema, thirst increased, upper extremity oedema.

Investigations: alkaline phosphatase increased, ALT increased, AST increased, bicarbonate decreased, blood pressure increased, blood urea nitrogen increased, creatine phosphokinase increased, erythrocytes increased, faecal occult blood, gamma glutamyl transpeptidase increased, leukocytes decreased, monocytes increased, non-specific ECG

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changes, platelets decreased, serum creatinine increased, uric acid increased, urine nitrite increased, weight gain.

Injury, poisoning and procedural complications: back strain, burn, contusion, corneal abrasion, knee sprain, laceration, strain, sunburn, trauma, traumatic arthropathy.

In one-year controlled clinical trials and in extension studies for up to 113 weeks (approximately 600 patients treated with ARCOXIA for one year or longer), the adverse experience profile was qualitatively similar to that observed in studies of shorter duration. The following additional serious adverse events have been reported rarely in at least two patients at an incidence of $\leq 0.2\%$ in patients taking ARCOXIA for up to 113 weeks, regardless of causality:

Infections and infestations: cellulitis.

Neoplasms benign, malignant and unspecified (including cysts and polyps): bladder malignant neoplasm.

Nervous system disorders: cerebrovascular accident, lacunar infarction.

Cardiac disorders: atrial fibrillation, cardiac arrest, coronary artery disease, myocardial infarction, unstable angina.

Vascular disorders: hypertensive crisis.

Gastrointestinal disorders: gastroduodenal ulcer, gastrointestinal bleeding.

Hepatobiliary disorders: cholecystitis.

Ankylosing Spondylitis

In a clinical study for ankylosing spondylitis, patients were treated with ARCOXIA 90mg once daily for up to 1 year (N=126). The following additional adverse experiences were seen in the 6-week placebo-controlled portion of the study at a rate $>2\%$, regardless of causality: dysgeusia, dyspepsia, pharyngitis, weight gain. 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.

Additional Safety Data from the MEDAL Program Studies

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 oedema occurred at similar rates on ARCOXIA 60mg compared to diclofenac; however, the incidences for these events were higher for ARCOXIA 90mg compared to diclofenac (see Table 2). The incidence of discontinuations due to atrial fibrillation was higher for etoricoxib compared to diclofenac (in OA patients: 0.8% versus 0.3 % for etoricoxib 90 mg and diclofenac respectively; 0.3 versus 0.2 for etoricoxib 60 mg versus diclofenac respectively).

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Table 2 Pre-specified Adverse Experiences of Interest by Disease and Dose

	Osteoarthritis 60mg		Osteoarthritis 90mg		Rheumatoid Arthritis	
	Etoricoxib 60mg (N=6769)	Diclofenac 150mg (N=6700)	Etoricoxib 90mg (N=2171)	Diclofenac 150mg (N=2162)	Etoricoxib 90mg (N=2841)	Diclofenac 150mg (N=2855)
Adverse Experience (AE)						
Confirmed congestive heart failure [†]	0.28 vs. 0.21 (p-Value 0.487)		0.69 vs. 0.32 (p-Value 0.133)		0.63 vs. 0.32 (p-Value 0.086)	
% of Patients Discontinued due to:						
Oedema-related AEs	0.83 vs. 0.73 (p-Value 0.557)		1.89 vs. 0.79 (p-Value 0.002)		0.99 vs. 0.56 (p-Value 0.071)	
Hypertension-related AEs	2.16 vs. 1.63 (p-Value 0.027)		2.53 vs. 1.11 (p-Value <0.001)		2.43 vs. 1.61 (p-Value 0.030)	
Hepatic-related AEs	0.33 vs. 1.78 (p-Value <0.001)		0.37 vs. 4.07 (p-Value <0.001)		0.42 vs. 1.68 (p-Value <0.001)	
Renal-related AEs	0.81 vs. 0.75 (p-Value 0.696)		2.30 vs. 1.80 (p-Value 0.284)		1.02 vs. 0.98 (p-Value 0.895)	
N = total number of patients; p-Values are for the difference between etoricoxib and diclofenac						
[†] Confirmed cases of CHF which were serious or resulted in discontinuation from the study and resulted in hospitalisation.						

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 7,111 patients with OA (EDGE Study; mean duration of treatment 9 months) and 4,086 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 oedema-related adverse experiences occurred at a higher rate on etoricoxib than on diclofenac. The rate of confirmed thrombotic cardiovascular serious adverse events occurring in the two treatment groups was similar.

Acute Gouty Arthritis

In a clinical study for acute gouty arthritis, patients were treated with ARCOXIA 120 mg once daily for eight days (N=75). The adverse experience profile in this study was generally similar to that reported in the combined OA, RA, and chronic low back pain studies.

Acute Pain

Approximately 1088 patients were treated with ARCOXIA 90 mg or 120 mg in acute analgesia studies. 191 patients in a multiple-dose post-dental surgery pain study were treated with ARCOXIA 90 mg once daily for up to 3 days. The adverse experience profile was generally similar to that reported in patients treated with ARCOXIA 120 mg in all acute analgesia studies. Patients in primary dysmenorrhoea and dental pain studies may have taken up to three daily doses of ARCOXIA, and those in the post-orthopaedic surgery pain study were prescribed seven daily doses of ARCOXIA.

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The adverse experience profile in the acute analgesia studies was generally similar to that reported in the combined OA, RA, and chronic low back pain studies. The following additional adverse experiences, which occurred at an incidence of at least 2% of patients treated with ARCOXIA, were observed in the post-dental pain surgery and primary dysmenorrhoea studies: dysgeusia, post-dental extraction alveolitis (dry socket).

In the 161 patients treated with ARCOXIA (average age approximately 65 years) in the post-orthopaedic surgery pain study, the most commonly reported adverse experiences were constipation, insomnia, and nausea.

Clinical Studies in OA, RA, AS and Chronic Low Back Pain with ARCOXIA 120 mg

In clinical trials of up to 12 weeks duration, the general safety profile of ARCOXIA 120 mg once daily (1.3 to 4 times the respective recommended doses of RA, AS, chronic low back pain and OA) was similar to that of ARCOXIA at the recommended doses of 30 or 60mg once daily in OA studies, 60 mg once daily in chronic low back pain studies and 90mg once daily in RA and AS studies. The following adverse experiences occurred at $\geq 2\%$ and at a higher incidence rate at 120 mg compared to 30 mg, 60 mg and 90 mg: abdominal pain, hypertension, dyspepsia, epigastric discomfort, heartburn, nausea and pharyngitis.

Post-marketing experience

The following adverse reactions have been reported in post-marketing experience:

Blood and lymphatic system disorders: thrombocytopenia.

Metabolism and nutrition disorders: hyperkalaemia.

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

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

Nervous system disorders: somnolence, dysgeusia.

Eye disorders: blurred vision.

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

Vascular disorders: hypertensive crisis.

Respiratory, thoracic and mediastinal disorders: bronchospasm.

Hepatobiliary disorders: hepatitis, jaundice, hepatic failure.

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

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

Renal and urinary disorders: renal insufficiency, including renal failure (see section 4.4).

The following serious undesirable effects have been reported in association with the use of NSAIDs and cannot be ruled out for etoricoxib: nephrotoxicity including interstitial nephritis and nephrotic syndrome, hepatotoxicity and pancreatitis.

Reporting of suspected adverse reactions

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Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>

4.9 Overdose

In clinical studies, administration of ARCOXIA at single doses up to 500mg and multiple doses up to 150mg/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 dialysable by haemodialysis; it is not known whether etoricoxib is dialysable by peritoneal dialysis.

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

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5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

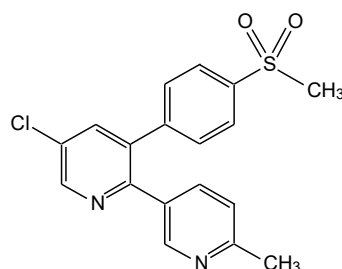
Pharmacotherapeutic group: Anti-inflammatory and antirheumatic products, non-steroids, coxibs.

ATC code: M01 AH05

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).

Chemistry

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.

Mechanism of Action

ARCOXIA is a 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 non-selective 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 150mg daily.

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The influence on gastro-protective COX-1 activity was also assessed in a clinical study where prostaglandin synthesis was measured in gastric biopsy samples from subjects administered either ARCOXIA 120mg daily, naproxen 500mg 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 150mg 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 500mg. There was no inhibition of *ex vivo* arachidonic acid or collagen induced platelet aggregation at steady state with doses of ARCOXIA up to 150mg. These findings are consistent with the COX-2 selectivity of etoricoxib.

5.2 Pharmacokinetic properties

Absorption

Orally administered etoricoxib is well absorbed. The mean oral bioavailability is approximately 100%. Following 120mg 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 $AUC_{0-24\text{ hr}}$ was 37.8 mcg \cdot hr/mL. The pharmacokinetics of etoricoxib are linear across the clinical dose range. In studies specifically designed to measure the onset of action of etoricoxib, the onset of action occurred as early as 24 minutes after dosing.

A standard meal had no clinically meaningful effect on the extent or rate of absorption of a dose of etoricoxib 120mg. 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-neutralising 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 ($V_{d_{ss}}$) 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 metabolised with <1% of a dose recovered in urine as the parent compound. The major route of metabolism to form the 6'-hydroxymethyl derivative is catalysed 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.

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Elimination

Following administration of a single 25mg radiolabelled intravenous dose of etoricoxib to healthy subjects, 70% of radioactivity was recovered in urine and 20% in faeces, mostly as metabolites. Less than 2% was recovered as unchanged etoricoxib. 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 120mg, 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

Gender

The pharmacokinetics of etoricoxib are similar between men and women (see section 4.2).

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 section 4.2).

Race

There is no clinically important effect of race on the pharmacokinetics of etoricoxib (see section 4.2).

Hepatic Insufficiency

Patients with mild hepatic insufficiency (Child-Pugh score 5-6) administered etoricoxib 60mg 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 60mg **every other day** had similar mean AUC to the healthy subjects given etoricoxib 60mg once daily; etoricoxib 30mg 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 section 4.2, Hepatic Insufficiency).

Renal Insufficiency

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

Paediatric Patients

The pharmacokinetics of etoricoxib in paediatric 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 60mg once daily and in adolescents >60 kg given etoricoxib 90mg once daily were similar to the pharmacokinetics in adults given etoricoxib 90mg once daily. Safety and effectiveness of etoricoxib in paediatric patients have not been established.

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Other

Clinical Trials

Osteoarthritis (OA)

Osteoarthritis patients treated with ARCOXIA had significant improvements in assessments of pain, inflammation, and mobility. Two double-blind, randomised clinical trials, lasting up to 52 weeks, were carried out in approximately 1,000 patients with OA flare of the knee or hip; hand OA was also assessed in 21% of patients. In both studies, ARCOXIA 60mg once daily demonstrated efficacy superior to placebo over a 12-week treatment period (see Table 3 for primary endpoint results) and comparable to naproxen 500mg twice daily throughout the 52-week treatment period. Patients showed significant reductions in pain, joint stiffness, joint tenderness, and significant improvement in mobility. Clinical efficacy was demonstrated within two days and continued for the duration of the studies. In patients with OA of the hand, reductions in pain and stiffness, and improvement in physical function, as measured by the AUSCAN questionnaire were superior to placebo and similar to that in patients treated with naproxen.

Table 3 Analyses of Primary Endpoints of Patients with Osteoarthritis Mean Change from Baseline (Over 12 Weeks)

LS Mean Change (Decrease) From Baseline¹			
	Placebo (n=111)	Etoricoxib 60mg (n=443) ²	Naproxen 1000mg (n=436) ²
Pain Subscale	-15.31	-27.94 ³	-28.57 ³
Physical Function Subscale	-10.27	-22.81 ³	-23.70 ³
Patient Global Assessment of Disease	-13.38	-26.39 ³	-26.46 ³
¹ LS = least square mean change from Baseline (change per 100 millimetres) using Western Ontario and McMasters Universities Assessment Tools (WOMAC). A negative change is associated with an improvement in the assessment parameter. ² In the Patient Global Assessment of Disease Activity, the total number of patients available for assessment in the Etoricoxib 60mg and Naproxen 1000mg treatment groups were 442 and 435, respectively. ³ P value of etoricoxib or naproxen versus placebo = <0.001.			

In a third study that enrolled approximately 600 patients, ARCOXIA 60mg once daily was superior to placebo over a six-week treatment period (using similar assessments as the first two studies) and was similar to diclofenac 50mg three times daily in patient assessment of response to study medication and investigator assessment of disease status over a treatment period of up to 92 weeks. ARCOXIA 60mg demonstrated significantly greater improvement than the 30mg dose for all 3 primary endpoints over 6 weeks of treatment.

In four additional studies that enrolled 913 patients, ARCOXIA 30mg once daily was superior to placebo over a twelve-week treatment period (using similar assessments as the above studies). In two of these studies, ARCOXIA 30mg once daily was comparable to ibuprofen

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2400mg daily (800mg three times daily) over the 12 week treatment period. In the other two studies, ARCOXIA 30mg once daily was comparable to celecoxib 200mg once daily over 12 and 26 weeks of treatment.

Rheumatoid Arthritis (RA)

Rheumatoid Arthritis patients treated with ARCOXIA had significant improvements in multiple assessments of pain, inflammation, and mobility. Approximately 1700 patients with RA were studied in two double-blind, clinical trials over 12-week treatment periods. ARCOXIA 90mg once daily demonstrated efficacy superior to placebo in both studies. In one study ARCOXIA demonstrated efficacy similar to naproxen 500mg twice daily, and in the other study demonstrated efficacy superior to naproxen. In these two studies, patients using ARCOXIA showed clinically significant reductions in the number of tender joints, number of swollen joints, and improvements in patient and investigator assessments of disease activity. ARCOXIA also showed improvement using the American College of Rheumatology 20% (ACR20) Responder Index, a composite of clinical, laboratory, and functional measures of RA. The beneficial effects of ARCOXIA were seen as early as two weeks (the first determination) and maintained for the duration of the studies.

In a third study that enrolled approximately 600 patients, ARCOXIA 90mg once daily demonstrated similar efficacy (using similar assessments as the first two studies) to diclofenac 50mg three times daily over a 44-week treatment period.

In a 12-week double-blind study evaluating the 60 mg dose compared to the 90 mg dose in 1404 patients with RA, both ARCOXIA 60 mg and 90 mg once daily demonstrated efficacy superior to placebo for change from baseline DAS28-CRP score and change from baseline PGAP score over a 6-week period. ARCOXIA 60 mg and 90 mg once daily provided similar overall effectiveness for change from baseline DAS28-CRP score. On post-hoc analysis, it was found that some patients, including patients with higher levels of pain as assessed by Patient Global Assessment of Pain (PGAP), may derive better pain relief with 90 mg once daily compared to 60 mg once daily.

Ankylosing Spondylitis (AS)

ARCOXIA has demonstrated significant improvements in spine pain, inflammation, stiffness, function and mobility. ARCOXIA was evaluated for the treatment of AS in a 52-week, two-part, double-blind, parallel group clinical trial that enrolled approximately 400 patients. In the 6-week placebo-controlled portion of the study, ARCOXIA 90mg once daily was superior to placebo on all primary endpoints (patient assessment of spine pain, patient assessment of disease activity and Bath AS Functional Index assessment). Additionally, ARCOXIA 90mg demonstrated statistically greater treatment effects than naproxen 500mg twice daily in patient assessment of spine pain and patient assessment of disease activity in the 6-week placebo-controlled portion of the study. The beneficial effects of ARCOXIA 90mg were maintained throughout the 52-week double-blind, active-comparator treatment period. ARCOXIA demonstrated statistically greater treatment effects than naproxen for assessments of spine pain, inflammation, stiffness and function for 1 year. The clinical benefit of etoricoxib was observed as early as 4 hours after initiation of treatment. A 120mg once daily dose of ARCOXIA was also studied; however, no additional efficacy was seen compared to the 90mg dose.

In a two-part, double-blind, parallel group clinical trial that enrolled 1015 patients, ARCOXIA 60 mg and 90 mg once daily demonstrated similar efficacy as compared to naproxen 500 mg twice daily on the primary endpoint of change from baseline in Spinal Pain Intensity score over the 6-week treatment period. There was no difference in the extent of improvement between 60 mg and 90 mg ARCOXIA for change from baseline Spinal Pain Intensity score,

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however, among inadequate responders to 60 mg daily for 6 weeks, dose escalation to 90 mg daily was statistically (though pre-determined Minimally Clinical Important Difference (MCID) was not met) more effective than continuing on 60 mg daily.

Acute Gouty Arthritis

ARCOXIA 120mg once daily, over an eight-day treatment period, demonstrated reductions in joint pain and inflammation (tenderness, swelling, and erythema) comparable to indomethacin 50mg three times daily in the treatment of patients experiencing moderate to extreme pain (approximately 150 patients) during an attack of acute gouty arthritis. Reduction in pain was observed as early as four hours after initiation of treatment (the first determination).

Acute Pain

In single-dose clinical studies which treated approximately 1200 patients, ARCOXIA relieved moderate-to-severe pain in acute analgesic models of post-operative dental pain and primary dysmenorrhoea. The analgesic effect of a 120mg dose of ARCOXIA was similar to a maximum analgesic dose of naproxen sodium (550mg) or ibuprofen (400mg) and greater than paracetamol (600mg) with codeine (60mg). The onset of analgesia with ARCOXIA occurred as early as 24 minutes after dosing and persisted for as long as 24 hours. In a multiple-dose clinical study of post-orthopaedic surgical pain, ARCOXIA 120mg once daily given for up to seven days was effective in relieving pain.

In a multiple-dose post dental surgery study (Protocol 092), ARCOXIA 90 mg administered once daily for up to three days provided a significantly greater analgesic effect compared to placebo. ARCOXIA 90mg provided a shorter time to onset and longer duration of pain relief, greater peak pain relief, in addition to a lower use of rescue analgesic medication following the initial first day dose compared to placebo. ARCOXIA 90 mg was non-inferior to ibuprofen 600 mg four times daily, and superior to paracetamol/codeine 600 mg/60 mg four times daily in total pain relief.

Chronic Musculoskeletal Pain

ARCOXIA relieved pain in studies of patients with chronic low back pain (approximately 650 patients). The analgesic effect of ARCOXIA was shown by measures of pain-related responses (e.g., pain symptoms, mobility, patient and investigator assessments of therapy). ARCOXIA 60mg once daily demonstrated significant efficacy within one week of treatment (the first determination). A reduction of chronic low back pain was maintained in patients treated with ARCOXIA over the 12-week, placebo-controlled treatment period.

Special Studies

Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) Study Program

The MEDAL Program was a prospectively designed Cardiovascular (CV) Safety Outcomes program of pooled data from three individual, randomised, double-blind active comparator (diclofenac) -controlled trials (MEDAL study, EDGE II and EDGE). The MEDAL Program also evaluated upper and lower GI safety. The Program consisted of 34,701 OA and RA patients treated with etoricoxib 60mg daily (OA) or etoricoxib 90mg daily (OA and RA, 1.5 to 3 times the doses recommended for OA) versus diclofenac 150mg daily for a mean period of approximately 18 months; approximately 12,800 had more than 24 months of exposure with some patients receiving up to 42 months of treatment.

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Patients enrolled in the MEDAL Program had a wide range of baseline cardiovascular and gastrointestinal risk factors. Approximately 47% of patients had a history of hypertension, approximately 12% had a history of symptomatic atherosclerotic cardiovascular disease (ASCVD) and approximately 38% of patients had an increased cardiovascular risk at baseline (defined as having either a previous history of symptomatic ASCVD or ≥ 2 Cardiovascular Risk Factors from among the following 5 [history of hypertension, history of diabetes mellitus, history of dyslipidaemia, family history of cardiovascular disease, cigarette use]). Patients with a recent history of myocardial infarction, coronary artery bypass grafting or percutaneous coronary intervention within 6 months preceding enrolment were excluded. Use of gastro-protective agents and low-dose aspirin were permitted in the studies with approximately 50% of the patients on gastro-protective agents and approximately 35% of the patients on low-dose aspirin. In the studies, efficacy of etoricoxib 60mg and 90mg was shown to be comparable to diclofenac.

The cardiovascular and gastrointestinal safety data are summarised below. Other important safety data, including renovascular data, is described in section 4.8.

Cardiovascular data: The MEDAL Program showed that the rates of confirmed thrombotic cardiovascular serious adverse events (consisting of cardiac, cerebrovascular, and peripheral vascular events) were comparable between etoricoxib and diclofenac (see Table 4). For the primary endpoint of confirmed thrombotic CV events, the relative risk between etoricoxib and diclofenac was 0.95 (95% CI: 0.81, 1.11) in the pre-specified primary analysis. The event rates for individual types of thrombotic events (e.g. myocardial infarction and stroke) were also similar between etoricoxib and diclofenac. The rates were similar between etoricoxib and diclofenac over the entire duration of the study, including in the subset of patients who were on treatment for greater than 24 months. There were no discernible differences in thrombotic event rates between etoricoxib and diclofenac across all subgroups analysed, including patient categories across a range of baseline cardiovascular risk. CV mortality, as well as overall mortality, was similar between the etoricoxib and diclofenac treatment groups.

Table 4 Overall Rates of Confirmed Thrombotic CV Events (Pooled MEDAL Program)

	Etoricoxib (N=16819)	Diclofenac (N=16483)	Between Treatment Comparison
	25836 Patient-Years	24766 Patient-Years	
	Rate[†] (95% CI)	Rate[†] (95% CI)	Relative Risk (95% CI)
Total number of patients with Endpoint	1.24 (1.11, 1.38)	1.30 (1.17, 1.45)	0.95 (0.81, 1.11)
Cardiac Events	0.71 (0.61, 0.82)	0.78 (0.68, 0.90)	0.90 (0.74, 1.10)
Cerebrovascular Events	0.34 (0.28, 0.42)	0.32 (0.25, 0.40)	1.08 (0.80, 1.46)
Peripheral Vascular	0.20 (0.15, 0.27)	0.22 (0.17, 0.29)	0.92 (0.63, 1.35)
† Events per 100 Patient-Years. N = total number of patients; CI=confidence interval			

Gastrointestinal data: Overall upper GI events were defined as perforations, ulcers and bleeds. The subset of overall upper GI events considered complicated included perforations, obstructions, and complicated bleeding; the subset of upper GI events considered uncomplicated included uncomplicated bleeds and uncomplicated ulcers. The rates per

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hundred patient-years of confirmed upper GI clinical events (perforations, ulcers, and bleeds; PUBs) were 0.67 (95% CI 0.57, 0.77) with etoricoxib and 0.97 (95% CI 0.85, 1.10) with diclofenac, yielding a relative risk of 0.69 (95% CI 0.57, 0.83). No significant difference was observed in rates of complicated upper GI clinical events between etoricoxib and diclofenac (0.30 vs. 0.32 per hundred patient-years). As the risk for upper GI events increases with age, the rate for these events in elderly patients was evaluated. The largest risk reduction was observed in patients ≥ 75 years of age; the rate per hundred patient-years for a confirmed upper GI event was lower for etoricoxib compared to diclofenac (1.35 [95% CI 0.94, 1.87] vs. 2.78 [95% CI 2.14, 3.56]). The rates for confirmed upper GI events in patients taking concomitant low-dose aspirin and/or gastro-protective agents were also evaluated and are presented in Table 5. The rates of confirmed lower GI clinical events were 0.32 (95% CI 0.25, 0.39) vs. 0.38 (95% CI 0.31, 0.46) per hundred patient-years for etoricoxib vs. diclofenac, yielding a relative risk of 0.84 (95% CI 0.63, 1.13).

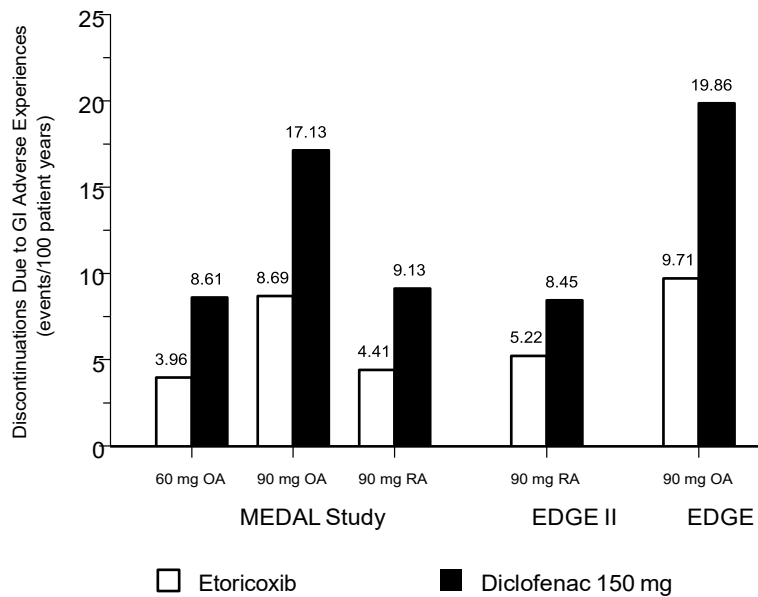
Table 5 Confirmed Upper GI Events (Pooled MEDAL Program)

	Etoricoxib	Diclofenac
	Rate [†] (95% CI)	Rate [†] (95% CI)
Overall Rate [Relative Risk 0.69 (0.57,0.83)]	0.67 (0.57, 0.77)	0.97 (0.85, 1.10)
Concomitant Low Dose Aspirin Use		
No	0.38 (0.29, 0.48)	0.73 (0.60, 0.87)
Yes	1.14 (0.94, 1.37)	1.37 (1.15, 1.63)
Concomitant Gastro-protective Agents Use[‡]		
No	0.63 (0.49, 0.79)	0.83 (0.67, 1.02)
Yes	0.70 (0.57, 0.84)	1.07 (0.91, 1.25)
[†] Rate = Events per 100 patient-years = (n/PYR)x 100. CI = Confidence Interval. [‡] Proton pump inhibitors and misoprostol accounted for approximately 96% of patients taking gastro-protective agents		

GI tolerability, defined as patients discontinuing the study for any clinical (e.g., dyspepsia, abdominal pain, ulcer) or laboratory (e.g., increased ALT, AST) GI adverse experience including hepatic events, was also evaluated in each individual study within the MEDAL Program. The EDGE and EDGE II studies assessed GI tolerability as the primary endpoint. They compared etoricoxib 90mg daily and diclofenac 150mg daily in patients with OA (EDGE) and RA (EDGE II). The MEDAL Study compared GI tolerability between etoricoxib 60mg (OA) or 90mg (OA and RA) to diclofenac 150mg daily as a secondary objective. In all three studies, etoricoxib demonstrated superior GI tolerability compared to diclofenac (p-values <0.001; See Figure 1). The GI tolerability benefit for etoricoxib was significant both for the clinical and for the laboratory components that make up this composite endpoint.

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Figure 1: GI Tolerability



Hepatic-related adverse events resulting in discontinuation were evaluated in each individual study within the MEDAL Program. The incidences of discontinuations were significantly lower in the etoricoxib 60 and 90mg treatment groups compared with the diclofenac 150mg treatment groups for both OA and RA patients in all three studies.

Additional Thrombotic Cardiovascular Safety Data

In a combined analysis of all 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 serious thrombotic cardiovascular events between patients receiving etoricoxib ≥ 30 mg or non-naproxen NSAIDs. However, the rate of these events was higher in patients receiving etoricoxib compared with those receiving naproxen 500mg twice daily, with a statistically significant increase in relative risk with etoricoxib with respect to the Anti-Platelet Trialists' Collaboration (APTCL) combined endpoint. In the studies which directly compared etoricoxib to placebo (6 to 12 weeks duration), there was no discernible difference in the event rates between patients receiving etoricoxib or placebo; however there were few events and the studies were limited in duration.

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**Table 6 Etoricoxib Development Program
Summary of Confirmed Thrombotic Events and Confirmed APTC Combined Endpoint**

Comparisons	N	n/PYR [†]	Rate [‡] (95% CI)	Relative Risk (95% CI)
Confirmed Thrombotic Events				
Etoricoxib	3940	9/810	1.11 (0.51, 2.11)	1.07 (0.36, 3.22)
Placebo	2337	5/450	1.11 (0.36, 2.59)	--
Etoricoxib	2147	14/1815	0.77 (0.42, 1.29)	0.73 (0.27, 1.98)
Non-Naproxen NSAIDs	1470	6/649	0.92 (0.34, 2.01)	--
Etoricoxib	1960	34/2480	1.37 (0.95, 1.92)	1.70 (0.91, 3.18)
Naproxen 1000mg	1497	14/1727	0.81 (0.44, 1.36)	--
Confirmed APTC Combined Endpoint				
Etoricoxib	3940	7/810	0.86 (0.35, 1.78)	1.95 (0.37, 19.19)
Placebo	2337	2/450	0.44 (0.05, 1.60)	--
Etoricoxib	2147	11/1817	0.61 (0.30, 1.08)	0.80 (0.25, 2.59)
Non-Naproxen NSAIDs	1470	4/649	0.62 (0.17, 1.58)	--
Etoricoxib	1960	27/2481	1.09 (0.72, 1.58)	2.72 (1.18, 6.27)
Naproxen 1000mg	1497	7/1728	0.41 (0.16, 0.83)	--
[†] Patient-years at risk. [‡] Per 100 PYR. APTC = Antiplatelet Trialists' Collaboration ; CI = Confidence interval; PYR = Patient-years at risk. APTC combined endpoint includes (cardiovascular, haemorrhagic and unknown death, non-fatal myocardial ischaemia, and non-fatal stroke).				

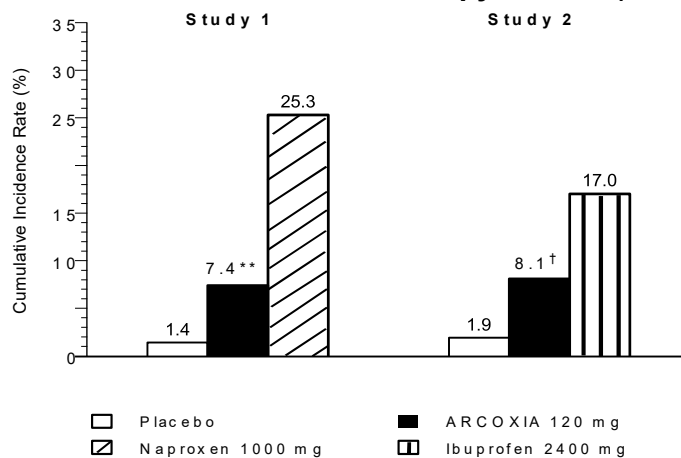
Additional Gastrointestinal Safety Data

The following special studies were conducted to evaluate whether ARCOXIA, a COX-2 selective inhibitor, is associated with less GI toxicity than non-selective NSAIDs.

Upper Endoscopy in Patients with Rheumatoid Arthritis or Osteoarthritis

The cumulative incidence of gastroduodenal ulcers was significantly lower in patients treated with ARCOXIA 120mg once daily than in patients treated with either of two non-selective NSAIDs (naproxen 500mg twice daily or ibuprofen 800mg three times daily) in two 12-week double-blind endoscopy studies. Seven hundred patients with either OA or RA were treated in Study 1, while 655 patients with OA were treated in Study 2. Patients treated with ARCOXIA had a higher cumulative incidence of ulcers as compared to patients treated with placebo (see Figure 2 for the results of these studies).

Figure 2 Life-Table Cumulative Incidence of Gastroduodenal Ulcer ≥ 3 mm* Over 12 Weeks for Both Endoscopy Studies (Intent-to-Treat)



* Results of analyses using a ≥ 5 mm gastroduodenal ulcer endpoint were consistent.

** $p < 0.001$ versus naproxen 500mg twice daily

† $p = 0.007$ versus ibuprofen 800mg three times daily.

Both endoscopy studies included the following patients at a higher risk for GI ulcers: patients with active *Helicobacter pylori* infection; baseline gastroduodenal erosions; prior history of perforation, ulcer or bleed (PUB); and/or concomitant use of corticosteroids. Four hundred patients (28%) were 65 years of age and older. The advantage of ARCOXIA versus naproxen or ibuprofen was maintained in these higher risk subgroups.

Gastrointestinal Safety Combined Analysis

In a combined analysis of all Phase IIb to V clinical studies of 4 weeks duration or longer (excluding the MEDAL Program Studies), the rate of PUB events (gastroduodenal perforations, symptomatic gastrointestinal ulcers or upper GI bleeds) for combined doses of etoricoxib ranging from 30mg to 120mg daily (N = 4,107 patients with a mean duration of treatment of approximately 220 days) was compared to non-selective NSAIDs (naproxen 1000mg daily, diclofenac 150mg daily and ibuprofen 2400mg daily; total N = 2,967 patients with a mean duration of treatment of approximately 182 days). The event rates of confirmed PUBs for the etoricoxib group were approximately half of those in the non-selective NSAIDs group during the first year of treatment (1.13 events per hundred-patient years for etoricoxib compared to 2.64 events per hundred patient-years for NSAIDs; relative risk 0.47 [95% CI: 0.28, 0.76]). The results were consistent over the entire follow-up period. In the combined analysis, the magnitude of the risk reduction for the complicated events (primarily a result of upper GI haemorrhages) was generally consistent over the entire treatment period with results for overall upper GI clinical events (relative risk 0.57 [95% CI: 0.31, 1.07]), although the number of events is more limited.

Gastrointestinal Clinical Tolerability Combined Analysis

A pre-specified, combined analysis of eight clinical trials of approximately 4,000 patients with OA, RA or chronic low back pain assessed the incidence rate for the following endpoints: 1) discontinuation for upper GI symptoms; 2) discontinuation for any GI adverse events; 3) new use of gastro-protective medications (including H2 receptor antagonists, misoprostol, and proton pump inhibitors); and 4) new use of any GI medications. There was an approximate 50% risk reduction for these endpoints in patients treated with ARCOXIA (60, 90 or 120mg daily) as compared to patients treated with non-selective NSAIDs (naproxen 500mg twice

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daily or diclofenac 50mg three times daily). There were no statistically significant differences between ARCOXIA and placebo.

Assessment of Faecal Occult Blood Loss in Healthy Subjects

To assess mucosal integrity throughout the gastrointestinal tract, faecal blood loss with ARCOXIA 120mg daily, ibuprofen 2400mg daily, and placebo was compared in a study utilising ⁵¹Cr-tagged red blood cells in 62 healthy males. After four weeks of treatment with ARCOXIA 120mg, there was no significant increase in the amount of faecal blood loss compared with placebo-treated subjects. In contrast, ibuprofen 2400mg daily produced a significant increase in faecal blood loss as compared to subjects treated with placebo and subjects treated with ARCOXIA.

Renal Function Study in Elderly Subjects

A randomised, double-blind, placebo-controlled, parallel-group study evaluated the effects of 15 days of treatment of etoricoxib (90mg), celecoxib (200mg twice daily), naproxen (500mg twice daily) and placebo on urinary sodium excretion, blood pressure, and other renal function parameters in subjects 60 to 85 years of age on a 200-mEq/day sodium diet. Etoricoxib, celecoxib, and naproxen had similar effects on urinary sodium excretion over the 2 weeks of treatment. All active comparators showed an increase relative to placebo with respect to systolic blood pressures; however, etoricoxib was associated with a statistically significant increase at Day 14 when compared to celecoxib and naproxen (mean change from baseline for systolic blood pressure: etoricoxib 7.7 mmHg, celecoxib 2.4 mmHg, naproxen 3.6 mmHg).

5.3 Preclinical safety data

Acute Toxicity

The approximate oral LD50 was 1499 mg/kg in both female mice and rats, while the intraperitoneal approximate oral LD50 was 599 mg/kg in female mice and 238 mg/kg in female rats. The approximate oral LD50 in rats and mice are >12 times the acute daily adult human dose [120 mg] based on systemic exposure.

Chronic Toxicity

The toxicity potential of etoricoxib was evaluated in a series of repeated-dose oral toxicity studies up to 53 weeks in dogs and rats. In each species, the principal treatment-related changes were associated with renal and gastrointestinal toxicity. Both the renal and gastrointestinal lesions were shown to occur at dosages above the intended chronic clinical dose of 90 mg daily.

In dogs administered etoricoxib orally at dosages of 200 mg/kg/day (approximately 20 times the daily adult human dose [90 mg] based on systemic exposure) for 14 weeks, toxicity was characterised by gastritis, gastrointestinal ulceration and renal papillary necrosis. No toxicity was seen in dogs administered 50 mg/kg/day (approximately 3 times the daily adult human dose based on systemic exposure) for 53 weeks.

In rats, etoricoxib administered orally at dosages of 30 mg/kg/day (approximately 3 times the daily adult human dose [90 mg] based on systemic exposure) following 27 weeks of administration produced gastrointestinal ulceration, as well as increased hepatic weights in female rats. At 53 weeks, the increased hepatic weights observed correlated with centrilobular hepatocellular hypertrophy due to hepatic CYP enzyme induction. No renal or gastrointestinal changes were noted in rats administered 10 mg/kg/day for 53 weeks (approximately equivalent to the daily adult human dose based on systemic exposure).

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Carcinogenicity

Etoricoxib was not carcinogenic in mice. Rats developed hepatocellular and thyroid follicular cell adenomas at >6 times the daily human dose [90 mg] based on systemic exposure when dosed daily for approximately 2 years. Tumours of these types are a species-specific consequence of hepatic CYP enzyme induction in the rat. These findings are consistent with other compounds associated with this induction. Etoricoxib has not been shown to cause hepatic CYP enzyme induction in humans.

Mutagenesis

Etoricoxib was found to be neither genotoxic nor mutagenic as described below. Etoricoxib was negative in the in vitro microbial and the TK6 human cell mutagenesis assays, with and without metabolic activation. There was no evidence of genotoxicity in the in vitro alkaline elution assay in rat hepatocytes and the in vitro chromosomal aberration assays in Chinese hamster ovary cells, with or without metabolic activation. In the in vivo alkaline elution/rat liver damage assays, etoricoxib did not induce DNA strand breaks in rat liver cells after oral administration of doses up to 300 mg/kg (1770 mg/m²; >20 times the daily adult dose [90 mg] based on systemic exposure). Similarly, there was no induction of chromosomal aberrations in bone marrow cells of male or female mice after the administration of oral doses of up to 1000 mg/kg (3000 mg/m²; approximately 10 times the daily adult dose [90 mg] based on systemic exposure).

Reproduction

In female rats administered etoricoxib, there were no adverse effects for maternotoxicity, fertility and embryonic/foetal survival at dosages of 10 mg/kg/day (approximately equivalent to the daily adult human dose [90mg] based on systemic exposure). At dosages of 30 mg/kg/day (approximately 3 times the daily adult human dose [90 mg] based on systemic exposure), there were treatment-related decreases in the number of implants.

High placental transfer of etoricoxib occurred in rabbits treated with 45 mg/kg/day (approximately 3 times the daily adult human dose [90 mg] based on systemic exposure), as evidenced by rabbit foetal plasma levels of approximately 60 to 70% of the mean maternal plasma medicine levels. In pregnant rats treated with 15 mg/kg/day (approximately 1.5 times the daily adult human dose [90 mg] based on systemic exposure), there was approximately 70 to 80% placental transfer of etoricoxib.

Significant concentrations of etoricoxib were observed in the milk of lactating rats. The mean milk concentrations of etoricoxib were approximately two-fold the mean maternal plasma concentrations in rats administered doses up to 15 mg/kg/day (approximately 1.5 times the daily adult human dose [90 mg] based on systemic exposure).

There were no treatment-related effects on mating performance, fertility indices, embryonic/foetal survival, sperm count, motility, testicular/epididymal organ weights, or histology in male rats administered dosages of etoricoxib up to 100 mg/kg/day (>6 times the daily adult human dose [90 mg] based on systemic exposure).

Development

No teratogenic effects were observed in rabbits and rats administered etoricoxib at doses up to 10 and 15 mg/kg/day, respectively (approximately equal to and approximately 1.5 times, respectively, the daily adult 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).

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6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Each tablet contains calcium hydrogen phosphate (anhydrous), carnauba wax, croscarmellose sodium, hypromellose, lactose (monohydrate), magnesium stearate, microcrystalline cellulose, titanium dioxide, and glycerol triacetate. The 30mg, 60mg and 120mg tablets also contain yellow ferric oxide (iron oxide yellow CI77492) and FD&C Blue #2 (indigo carmine [lake] CI73015).

6.2 Incompatibilities

Not Applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store below 30°C . Store in the original package.

6.5 Nature and contents of container

ARCOXIA 30mg tablets are currently not available in New Zealand.

ARCOXIA 60mg tablets are available in packs of 5 tablets (sample pack only not for sale) and 30 tablets.

ARCOXIA 90mg tablets are available in packs of 30 tablets.

ARCOXIA 120mg tablets are available in packs of 2 tablets (sample pack only not for sale) and 10 tablets.

6.6 Special precautions for disposal

None.

7 MEDICINE SCHEDULE

Prescription Medicine.

8 SPONSOR

Organon New Zealand Limited

P O Box 99-851

Newmarket

Auckland

NEW ZEALAND

Tel: 0800 111 700

9 DATE OF FIRST APPROVAL

24 October 2002

10 DATE OF REVISION OF THE TEXT

1 December 2020

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SUMMARY TABLE OF CHANGES

Sections Revised	Brief Description of Change
8	Amend sponsor details due to transfer of sponsorship